Pulmonary hypertension-
the rheumatologist's perspective

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Government of South Australia
SA Health

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INternational SYstemic sclerosis iNception Cohort

Disclosures

- Actelion Pharmaceuticals Australia
  - Chair, Actelion Clinical Excellence Program
  - Advisory board member

- Australian Scleroderma Interest Group is supported by unrestricted educational grants from
  - Actelion, Bayer, CSL, GSK and Pfizer

- PI for industry sponsored studies
  - Bayer
  - Boehringer Ingelheim

Case study

Referral from respiratory physician:

Diagnosis: COPD/??scleroderma

"Thank you for seeing this man with severe COPD, mod. pulm HT. ?

?sclerodactyly. Has Raynaud's, I think.

?scleroderma. ?

+ve ANA 1/2560 but -ve ENA"

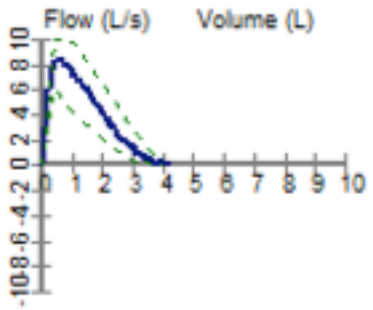
Case study

- 60 year old retired horse trainer
  - Smoker 30 pack years until 2013
  - 3 standard drinks/week
- Past history:
  - Testicular cancer 1987
  - Multiple fractures
- Progressive exertional dyspnoea (FC II)
  - On walking up hills
  - Able to perform ADLs
  - Productive cough in the mornings
  - Using portable oxygen concentrator
- Medications
  - Ranitidine 300mg/d
  - Triotropium 18mcg daily, Seretide, DuroTuss, Salbutamol

Pulmonary function tests

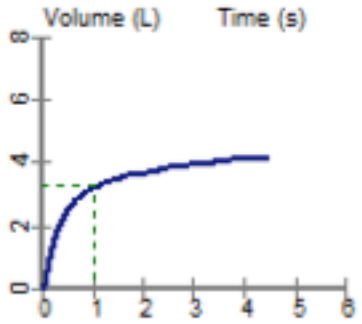
FORCED EXPIRATORY VOLUMES (BTPS) **[11:28]**

		Pre BD	Post BD	%Change	Predicted Mean (Range)
FEV_1	(L)	3.18 (100%)*	3.27 (103%)*	3%	3.19 (>2.48)
FVC	(L)	4.04 (96%)*	4.20 (100%)*	4%	4.21 (>3.37)
FEV_1 /FVC		79%	78%		76% (>66%)
FEF_{25-75}	(L/s)	2.83	2.89	2%	2.67 (>1.22)



SINGLE BREATH DIFFUSING CAPACITY **[11:49]**

		Observed		Predicted Mean (Range)
D_LCO uncorrected	(mL/min/mmHg)	6.7		26.3 (19.4-33.2)
D_LCO corrected for Hb	(mL/min/mmHg)	6.8	(26%)*	26.3 (19.4-33.2)
D_LCO/V_A corrected for Hb	(min/mmHg)	1.4		5.3 (4.0-6.6)
V_A	(L)	4.8		6.4 (5.3-7.6)

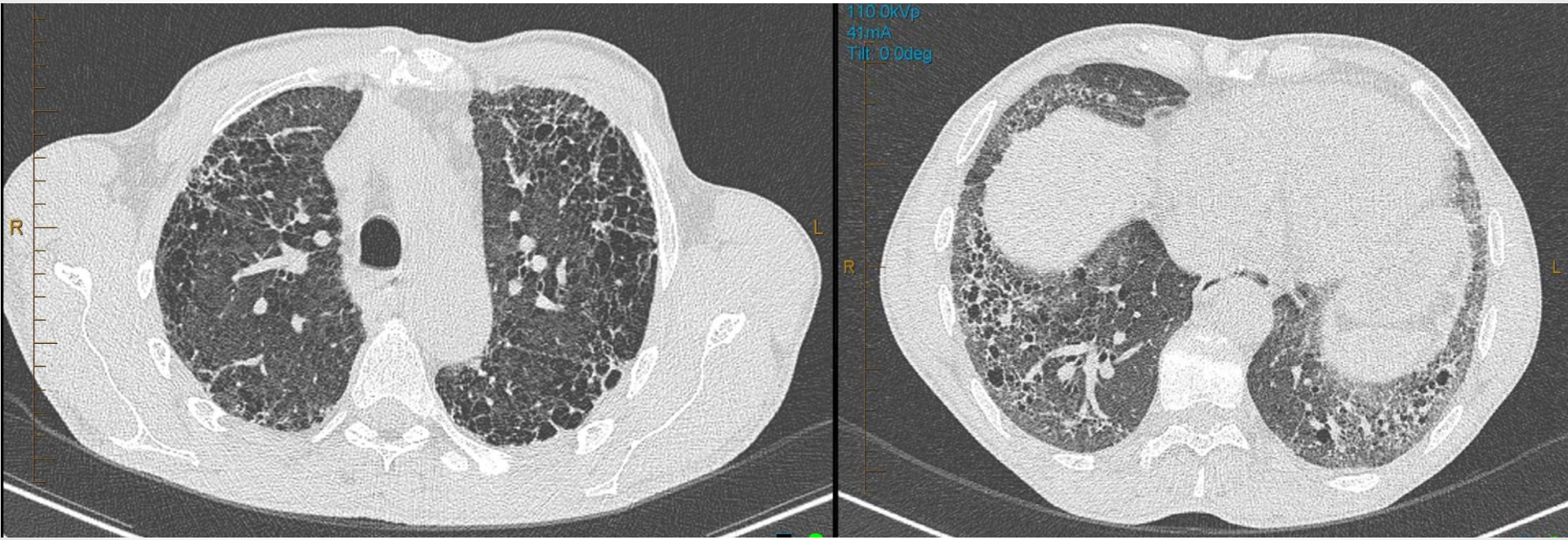


ARTERIAL BLOOD GASES **[11:16]**

At rest breathing room air		Observed	Predicted (Range)
PaO_2	(mmHg)	70	(75-91)
$PaCO_2$	(mmHg)	34	(36-44)
$[H^+]$	(nmol/L)	41	(36-44)
pH		7.39	(7.36-7.44)
Est. $[HCO_3^-]$	(mmol/L)	20	(22-31)
$P(A\text{-}a)O_2$	(mmHg)	38	(8-22)
Hb	(g/L)	138	(135-175)
COHb	(%)	1.8	(<2.0)

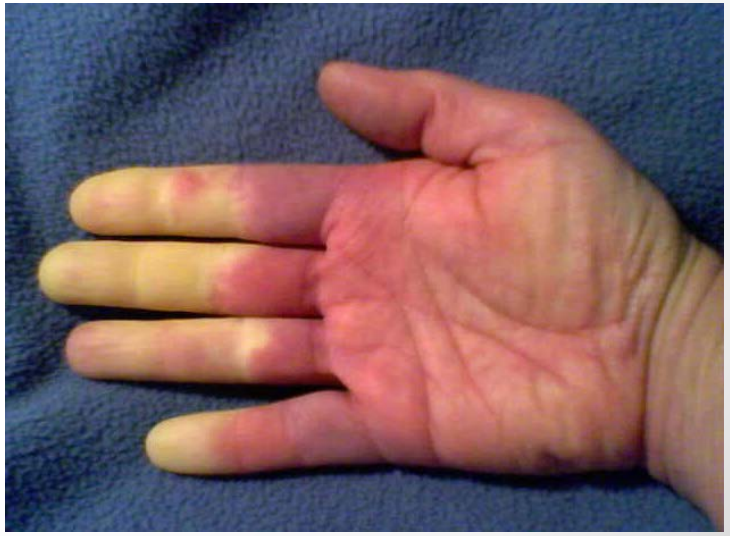
6 minute walk test: 483m, O_2 sats pre- 97%, post- 81%

HRCT scan – severe emphysema and progressive changes of usual interstitial pneumonia (UIP)



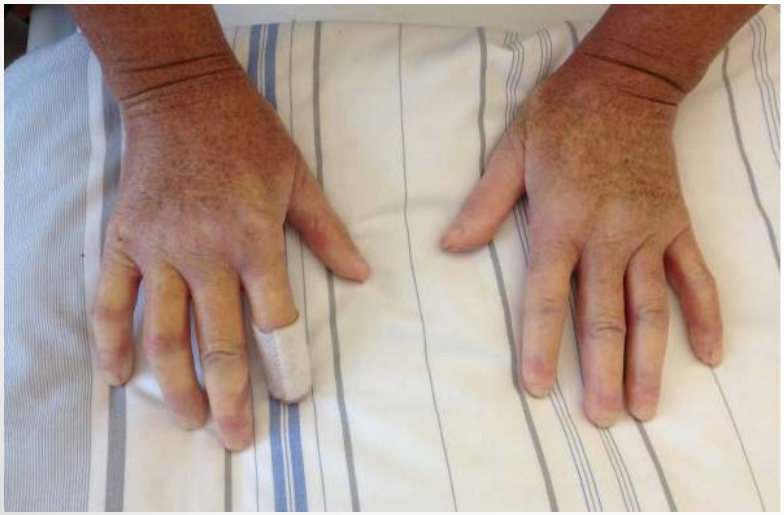
Additional history

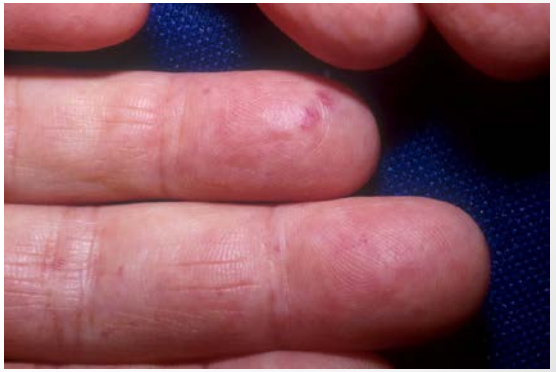
- Cold-induced biphasic colour change of fingers for 18 months
- Puffy fingers, reduced dexterity
- Dysphagia and heartburn, diarrhoea
- Impotence



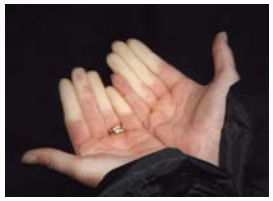
Examination

- BP125/80, HR 72 reg
- JVP↑ 5 cm, RV heave, loud P2, no SOA
- Fine bibasal crackles, ↓breath sounds generally
- Pulp atrophy, sclerodactyly, telangiectasiae
- Dilated nailfold capillaries with haemorrhages





Is it "pathological" Raynaud's Phenomenon - due to vasculopathy?



Reversible vasoconstriction

↓

Irreversible vasoconstriction

↓

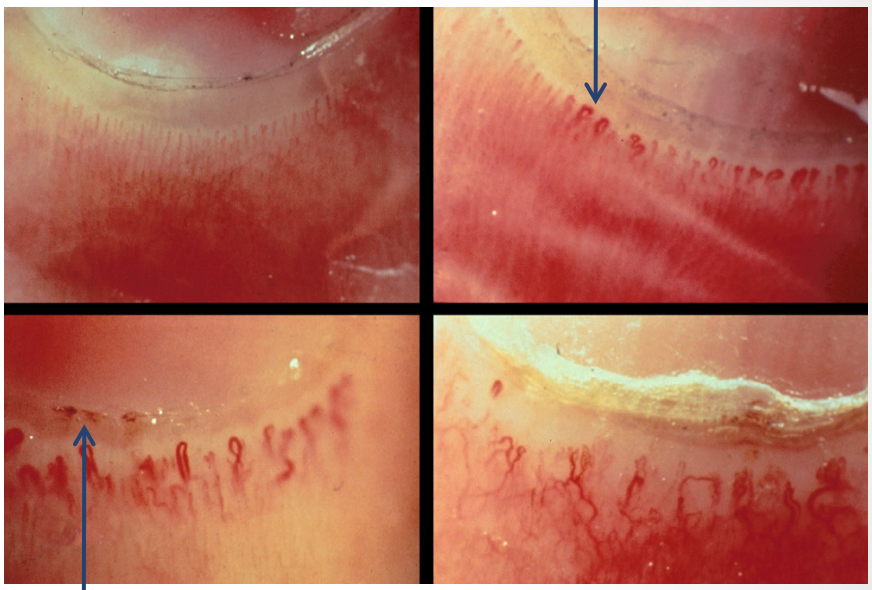
Capillary "drop out"

↓

Compensatory vasodilatation

↓

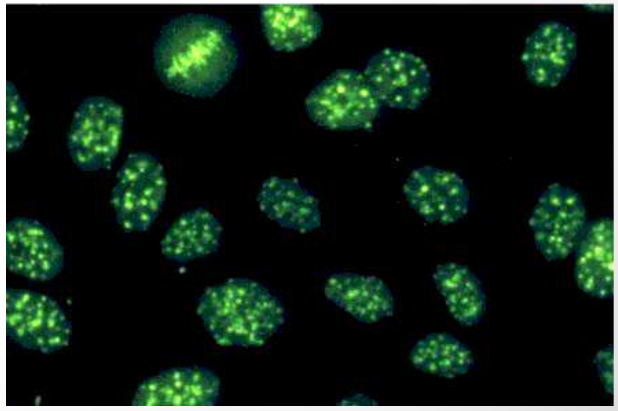
Loss of normal capillary arcade



nailfold capillaroscopy

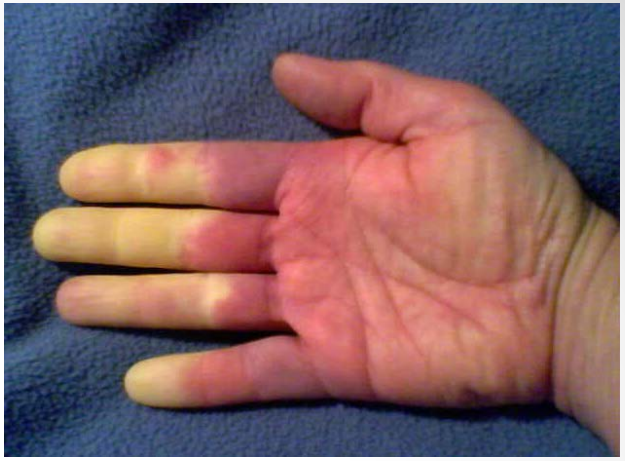
Additional investigations

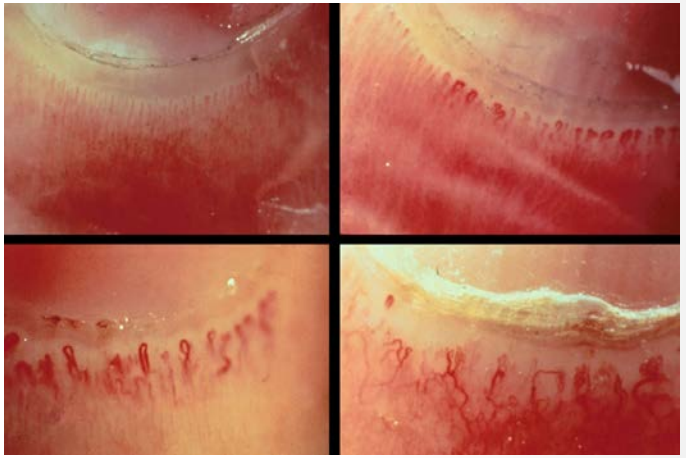
- Hb 133, U&E/LFT✓ ESR 1
- **ANA 1/2560 speckled**
- ENA/dsDNA/RF-ve
- ANCA+ PR3/MPO -ve
- alpha-1 anti-trypsin✓
- troponin <20

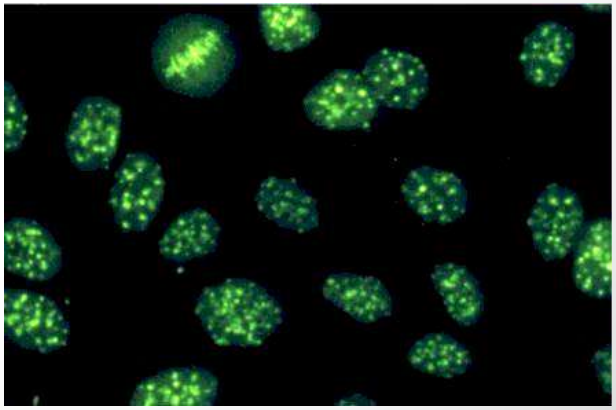


Could this be an autoimmune connective tissue disease?

COPD and pulmonary fibrosis



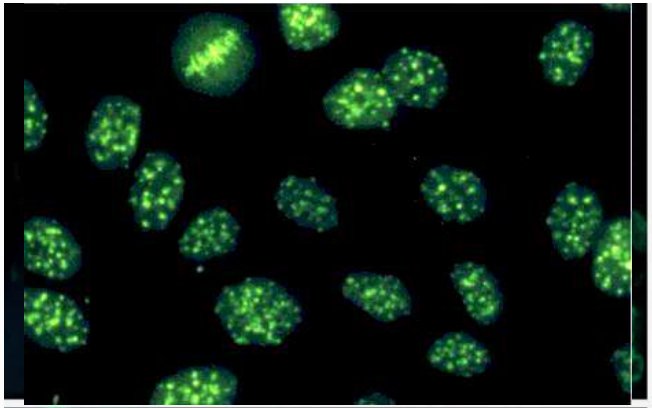


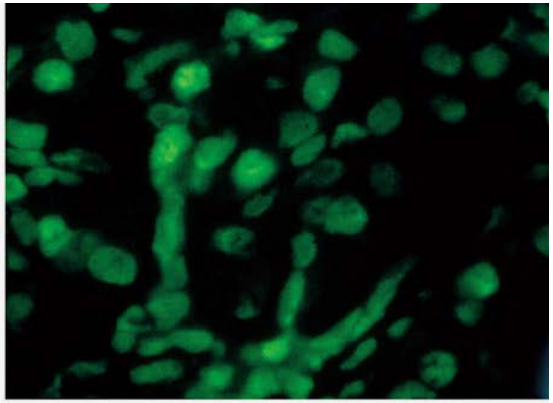


Antinuclear antibodies (ANA) – autoimmune tendency

Nonspecific screening test for autoimmune disease
Immunofluorescence: pattern and titre
1/40, 1/160, 1/640, 1/1280, 1/2560

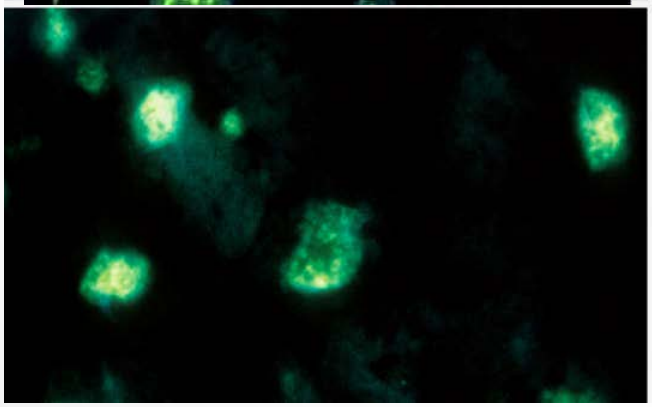
Centromere*

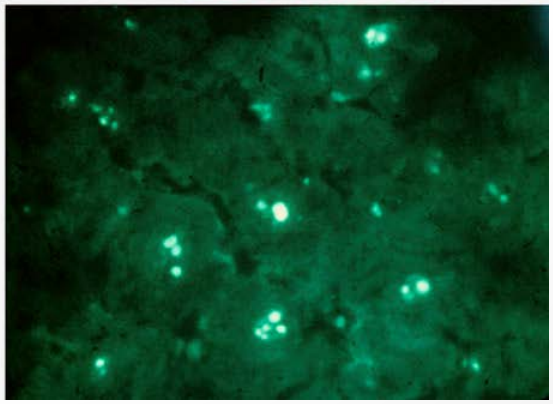




homogeneous

speckled

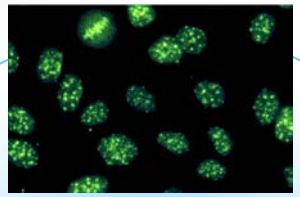


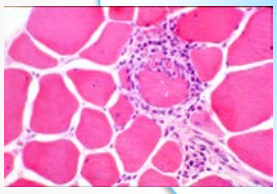


nucleolar*

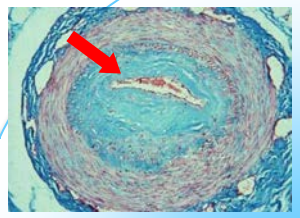
* Associated with systemic sclerosis

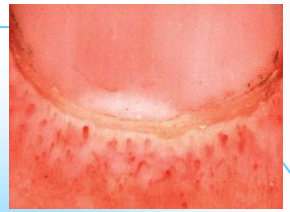
Systemic sclerosis (SSc): A heterogeneous, multiorgan disease

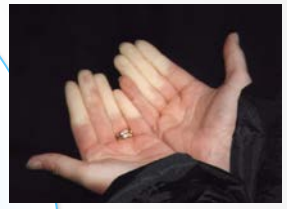




Inflammation

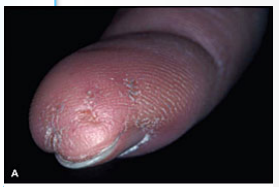


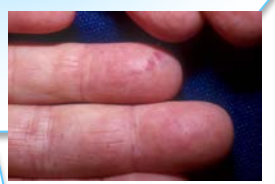


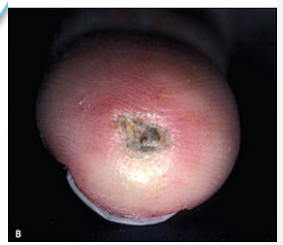


Vasculopathy

Gastric Antral
Vascular Ectasia



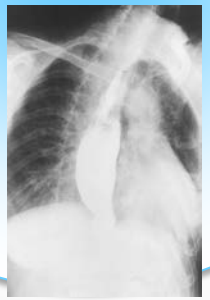


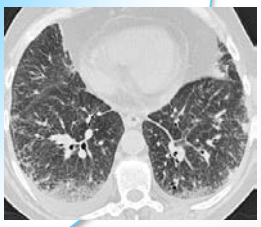


Renal PAH

Cardiac

Interstitial fibrosis





Fibrosis - thickened, tight skin
Begins on fingers, spreads proximally
Abnormal fibroblast production of Type I collagen with accumulation of glycosaminoglycan and fibronectin in the extracellular matrix
All skin is abnormal

Vasoconstriction – Raynaud's
Defective hypoxia response
Aberrant vascular remodelling, mediated by endothelin-1

Anti-RNA polymerase III autoantibody

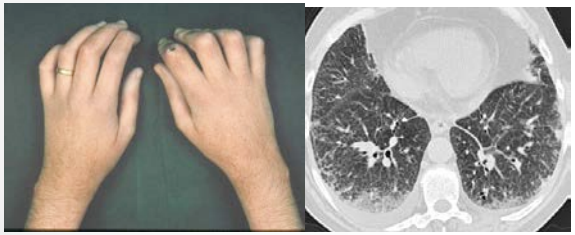
- The "third" SSc-specific autoantibody
- RNA polymerase III is a complex, 16-subunit enzyme directing transcription of small, stable nontranslated RNA genes: tRNAs, 5S rRNA, Alu-RNA and U6 7SK snRNA genes.
- Autoantibodies to RNA polymerase III are found in 11% to 23% of patients with SSc
- Associated with increased risk of diffuse SSc subset, more extensive skin disease & scleroderma renal crisis.
- Increased malignancy within 2 years of diagnosis of SSc

Systemic sclerosis subsets – defined by extent of skin involvement

Diffuse cutaneous SSc (dSSc)

Raynaud's…... short history
Rapid onset skin changes
Truncal and acral skin
Dilated nailfold capillaries
Tendon friction rubs

Early onset internal organ involvement (interstitial lung disease, renal crisis)

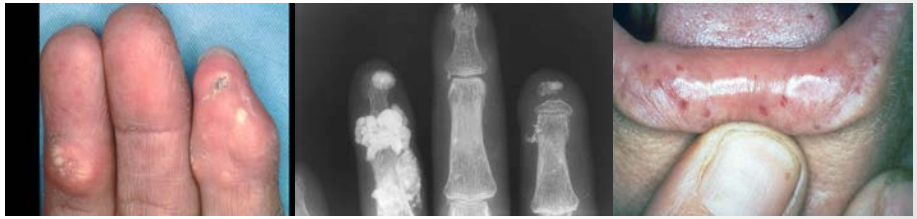


Scl-70 antibodies (anti-topoisomerase 1)
Anti-RNA polymerase I, III antibodies
ANA with nucleolar pattern

*Limited cutaneous SSc (lSSc)**

Raynaud's……. years
Gradual onset **S**kin changes limited to upper limbs, face
Dilated nailfold capillaries
Calcinosis, **T**elangiectasia

O**E**sophageal dysmotility
Clinically significant interstitial lung disease less frequent



Anti-centromere
A lower incidence of Scl-70

*previously known as **CREST** syndrome

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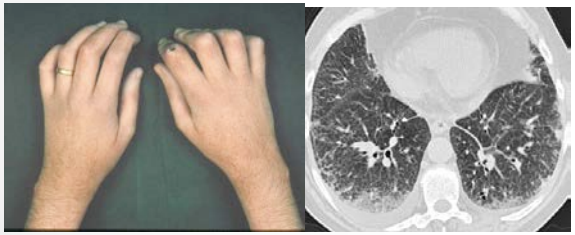

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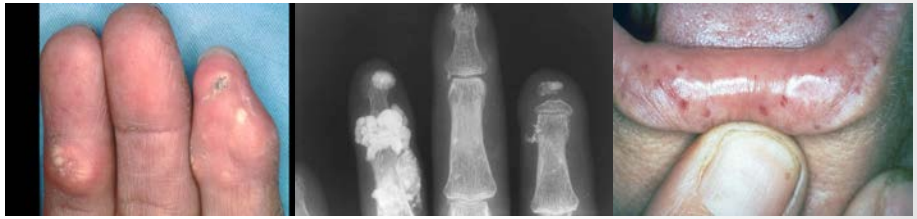

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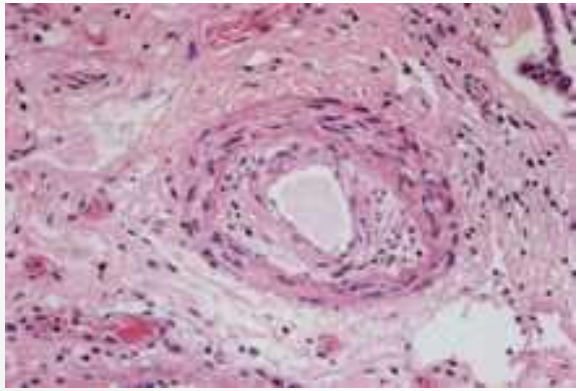
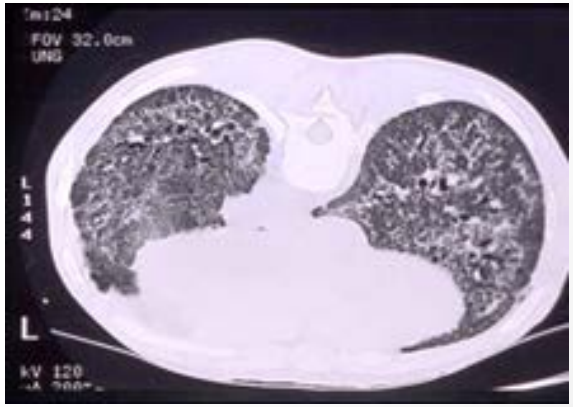
SSc Interstitial Lung Disease

- Pulmonary function is abnormal in 70% of patients
- Not all patients with ILD progress
- 70% with clinically significant ILD have diffuse SSc
- Diagnosis: high resolution CT scan chest
- Non Specific Interstitial Pneumonitis >> Usual Interstitial Pneumonitis
- Major contributor to morbidity and mortality in SSc
- May lead to PAH or co-exist with PAH (worse prognosis)
- Men with combined ILD and emphysema have the worst prognosis



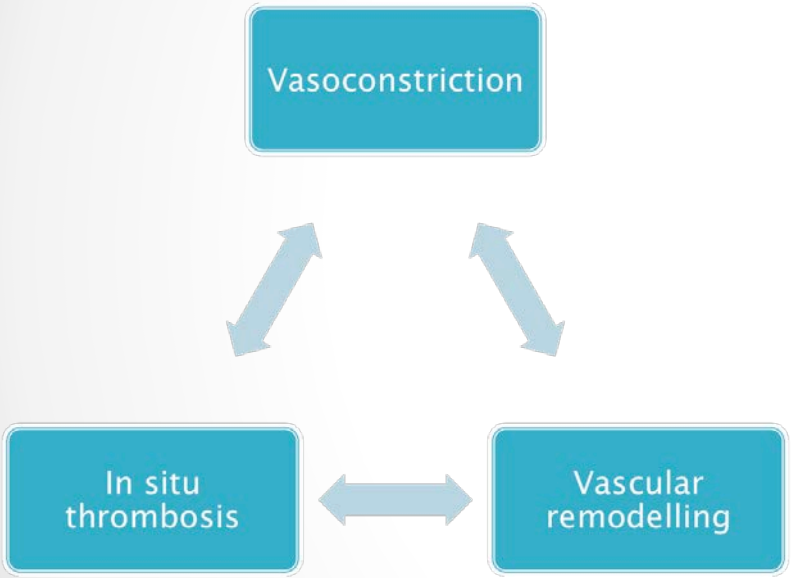


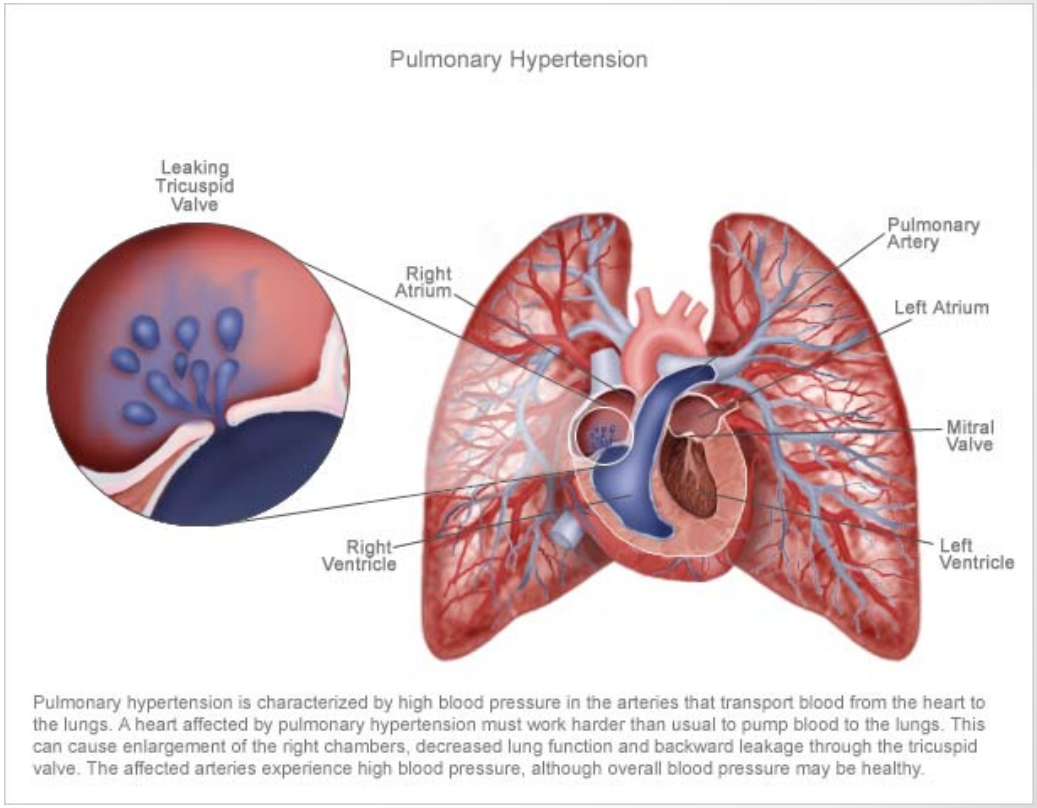
Owens G et al. Chest, 1983;84:546
Sahhar J et al. IMJ 2004;34:626

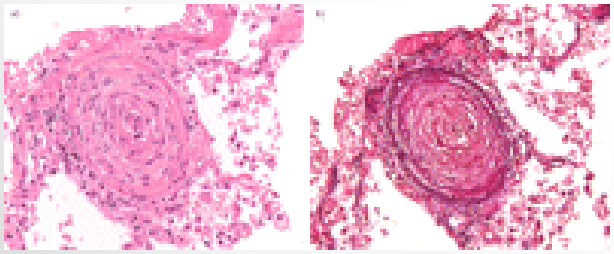
Is this pulmonary (arterial) hypertension?

Because the patient with SSc is known to be at risk for PAH, there is a unique opportunity to detect PAH earlier than in other cohorts

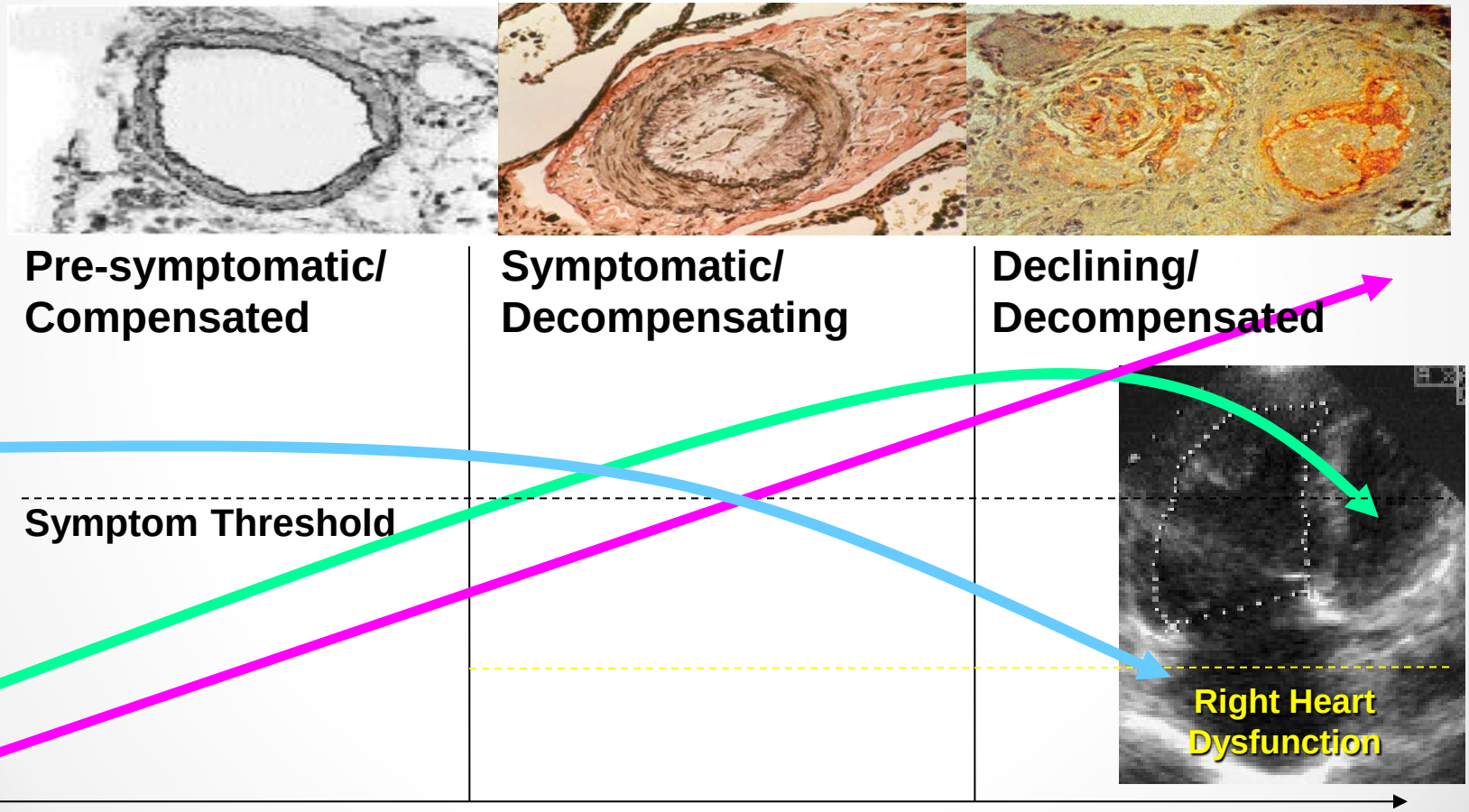
Pulmonary arterial hypertension- a disease of increasing pulmonary vascular resistance





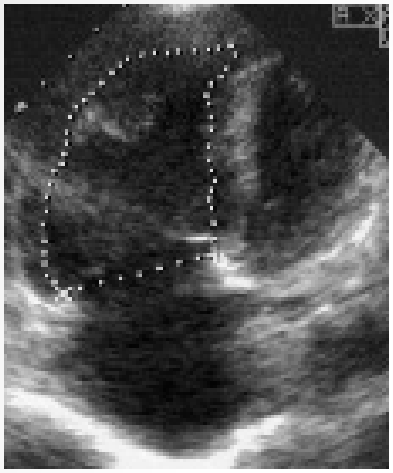


Schematic Progression of PAH

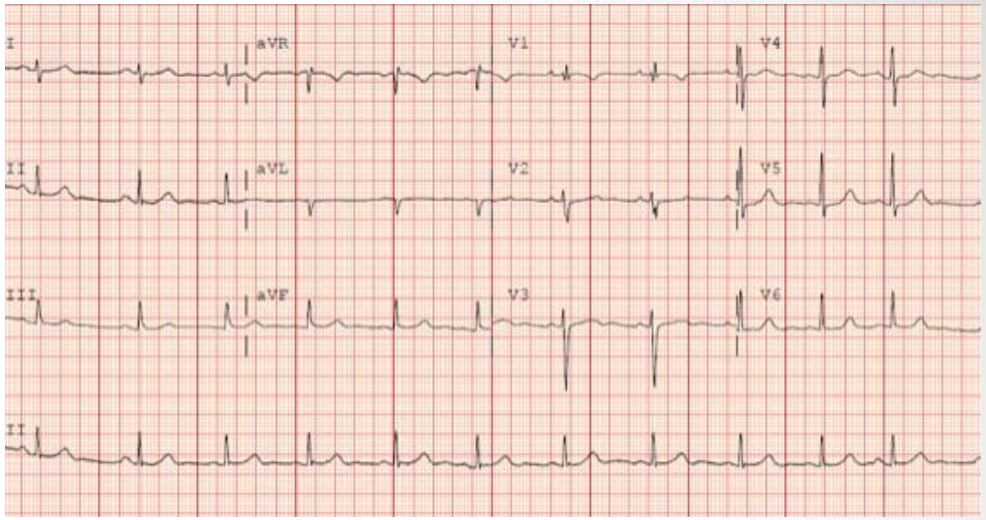


Rich S. Progress in Cardiovascular Diseases (Nov-Dec 1988); 31(3): 205-238

Echocardiogram



- LV✓ EF ~66 (BP)
- Grade 1 diastolic dysfunction
- Mildly abnormal LA volume.
- Mildly dilated RA.
- Dilated RV, low normal/mildly impaired RV systolic function.
- TR mild-mod. est systolic PAP 57mmHg (assuming RAP 8mmHg).
- Dilated IVC with collapse.



ECG

Sinus rhythm, right axis deviation

Diagnosing Pulmonary Hypertension

Echocardiography is non-invasive but can be unreliable

- Sensitivity (88%); Specificity (83%)
- Peak tricuspid regurgitant velocity (TRV) is used to calculate a systolic pressure gradient between RA and RV
- RA pressure (RAP) is estimated using IVC size and collapsibility of the RA
- RAP + RA-RV pressure gradient = RV systolic pressure (RVSP)
- RVSP is considered analogous to sPAP

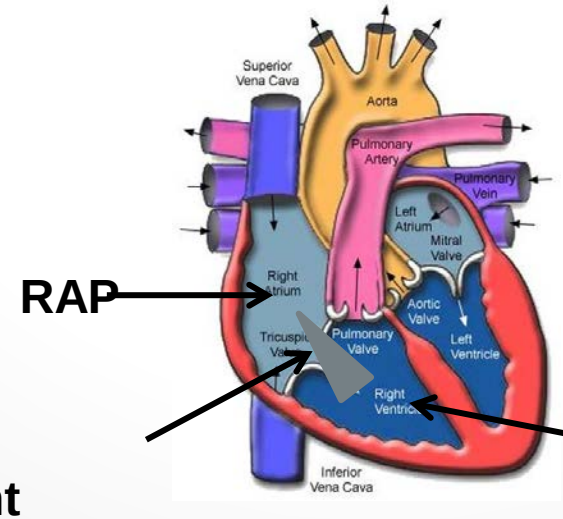
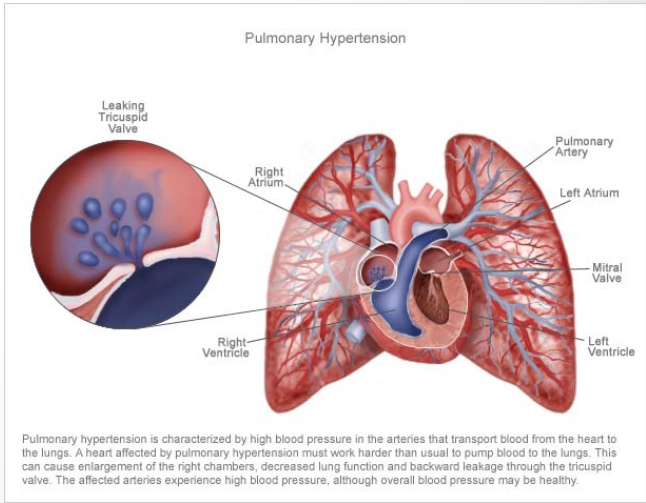


Image modified from:
http://founderspe.weebly.com/uploads/7/8/1/9/7819615/694534.jpg?487.

Right and left heart catheterisation

RHC is the 'gold standard' for definitive diagnosis of PAH:

- mean right atrial pressure (RAP) 13 mmHg
- mean pulmonary arterial pressure (mPAP) 34 mmHg
- pulmonary capillary wedge pressure (PCWP*) 14 mmHg
- transpulmonary gradient (mPAP-PCWP) = 20 mmHg
- cardiac index 3.45 L/min/m^2
- pulmonary vascular resistance (PVR) 3.32 Wood Units
- no shunt
- trivial coronary artery disease



*Now known as pulmonary arterial wedge pressure (PAWP)

Table 3 Haemodynamic definitions of pulmonary hypertension[a]

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

NB: “Exercise PH” removed

ESC/ERS Guidelines,
Galie et al. European Heart Journal 2015

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK4 mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

ESC/ERS Guidelines,
Galie et al. European Heart Journal 2015

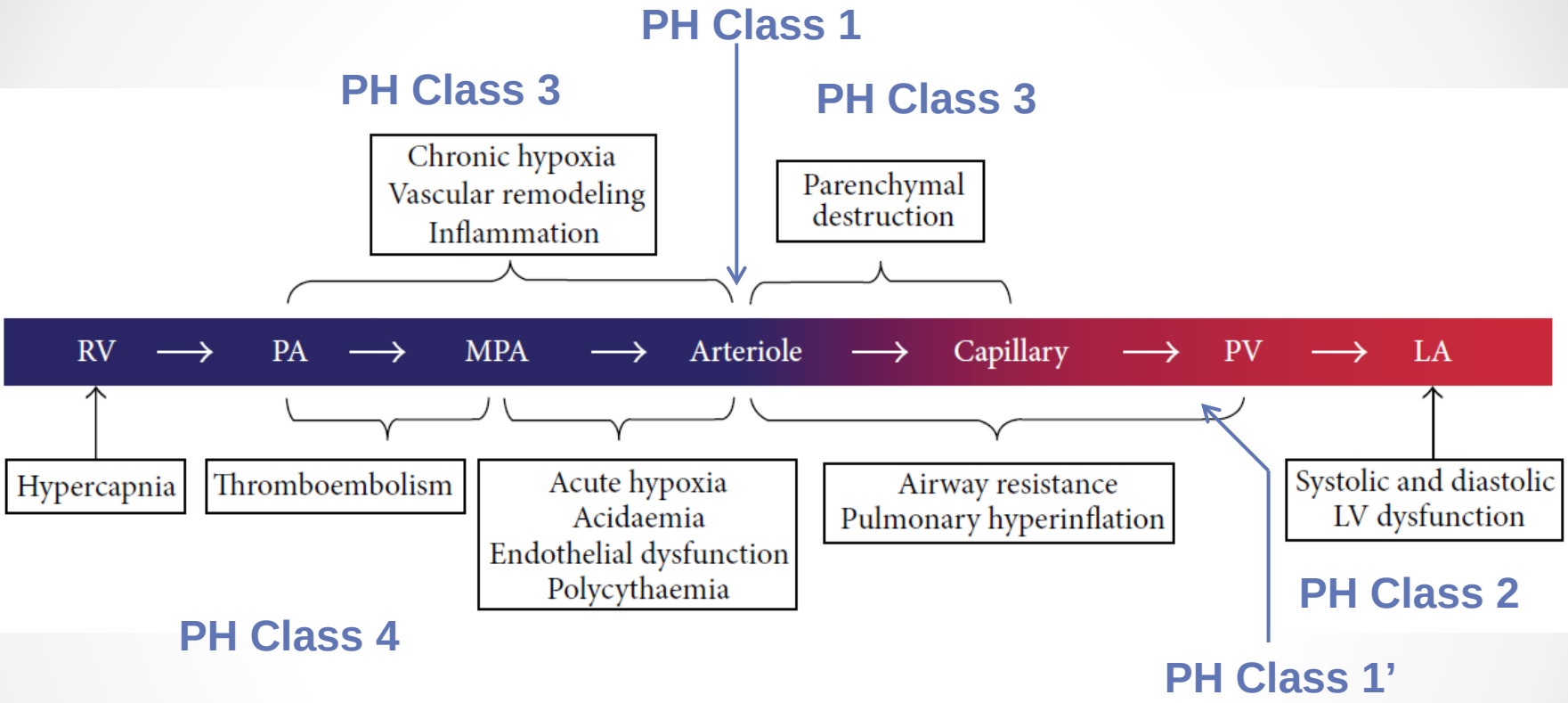
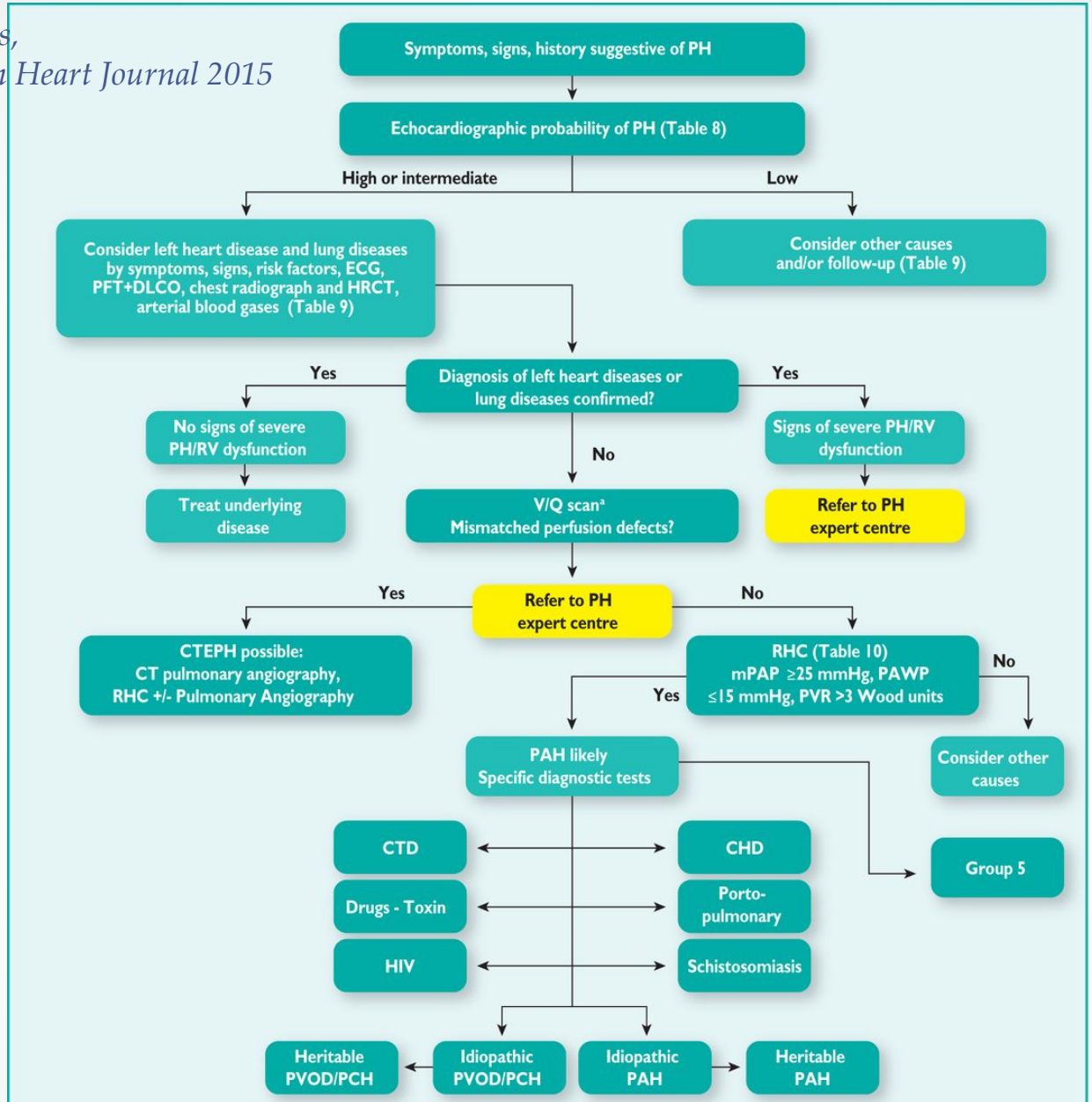


Image modified from: Zangiabadi A, De Pasquale CG, Sajkov D. Pulmonary hypertension and right heart dysfunction in chronic lung disease. Biomed Res Int. 2014;2014:739674.

ESC/ERS Guidelines,
Galie et al. European Heart Journal 2015



CHD = congenital heart diseases; CT = computed tomography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = carbon monoxide diffusing capacity; ECG = electrocardiogram; HIV = Human immunodeficiency virus; HR-CT = high resolution CT; mPAP = mean pulmonary arterial pressure; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function tests; PH = pulmonary hypertension; PVOD/PCH = pulmonary veno-occlusive disease or pulmonary capillary hemangiomathosis; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; RV = right ventricular; V/Q = ventilation/perfusion.

[a]CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

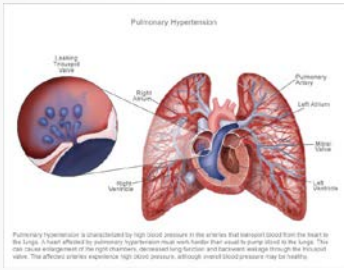
Cause of pulmonary hypertension?

- VQ scan:
  - Multiple mismatched perfusion defects scattered throughout all lobes of both lungs consistent with extensive pulmonary emboli. L>R
- lupus anticoagulant +ve
- beta 2 glycoprotein 1-ve, cardiolipin IgG –ve
- anti-thrombin III, Protein C & S – normal
- HIV-ve, TFTs✓
- No OSA?

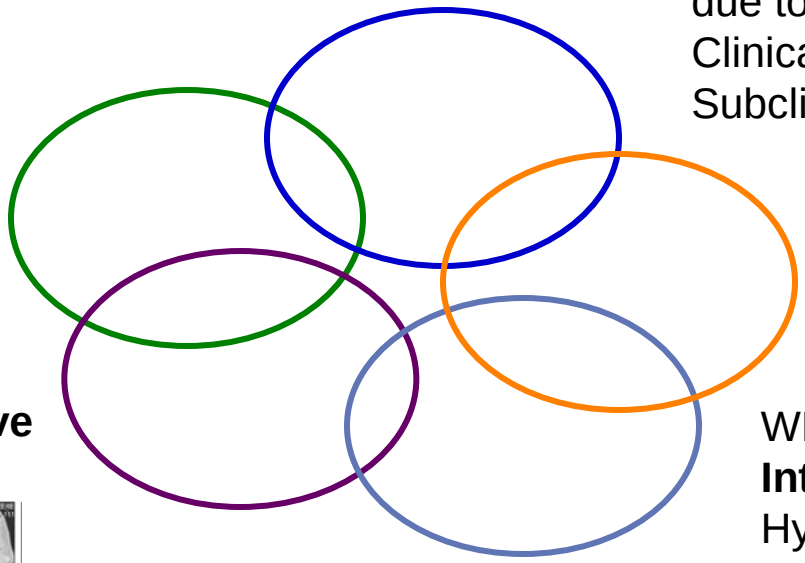
- CTPA:
  - no evidence of emboli or intimal webs to indicate acute or chronic embolic disease.
  - Perfusion maps indicate relative underperfusion of areas of fibrosis

Differential diagnosis of "pulmonary hypertension" in systemic sclerosis

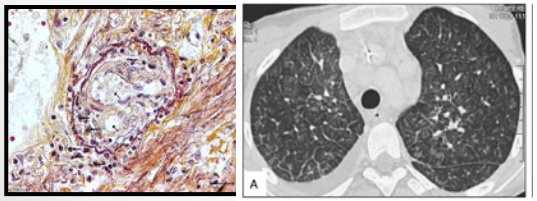
WHO Type 1.4.1
Pulmonary arterial hypertension (SSc-PAH)



WHO Type 2:
Pulmonary venous hypertension due to L heart disease – systolic or diastolic[#] dysfunction due to myocardial involvement*
Clinically evident in 15-35%
Subclinical in up to 75%

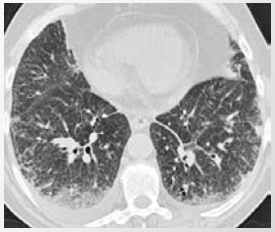


Pulmonary veno-occlusive disease (PVOD)



WHO Type 4:
Chronic thromboembolic pulmonary hypertension (CTEPH)
Antiphospholipid antibodies

WHO Type 3.2:
Interstitial lung disease (ILD)
Hypoxia, FVC <65%
HRCT chest >20% fibrosis



[#]Diastolic dysfunction (PCWP>15mmHg on RHC) is more common in older women with systemic hypertension, prior renal crisis and exercise induced PH
*also pericardial effusion, arrhythmias, conduction defects.

Prevalence of SSc-PAH

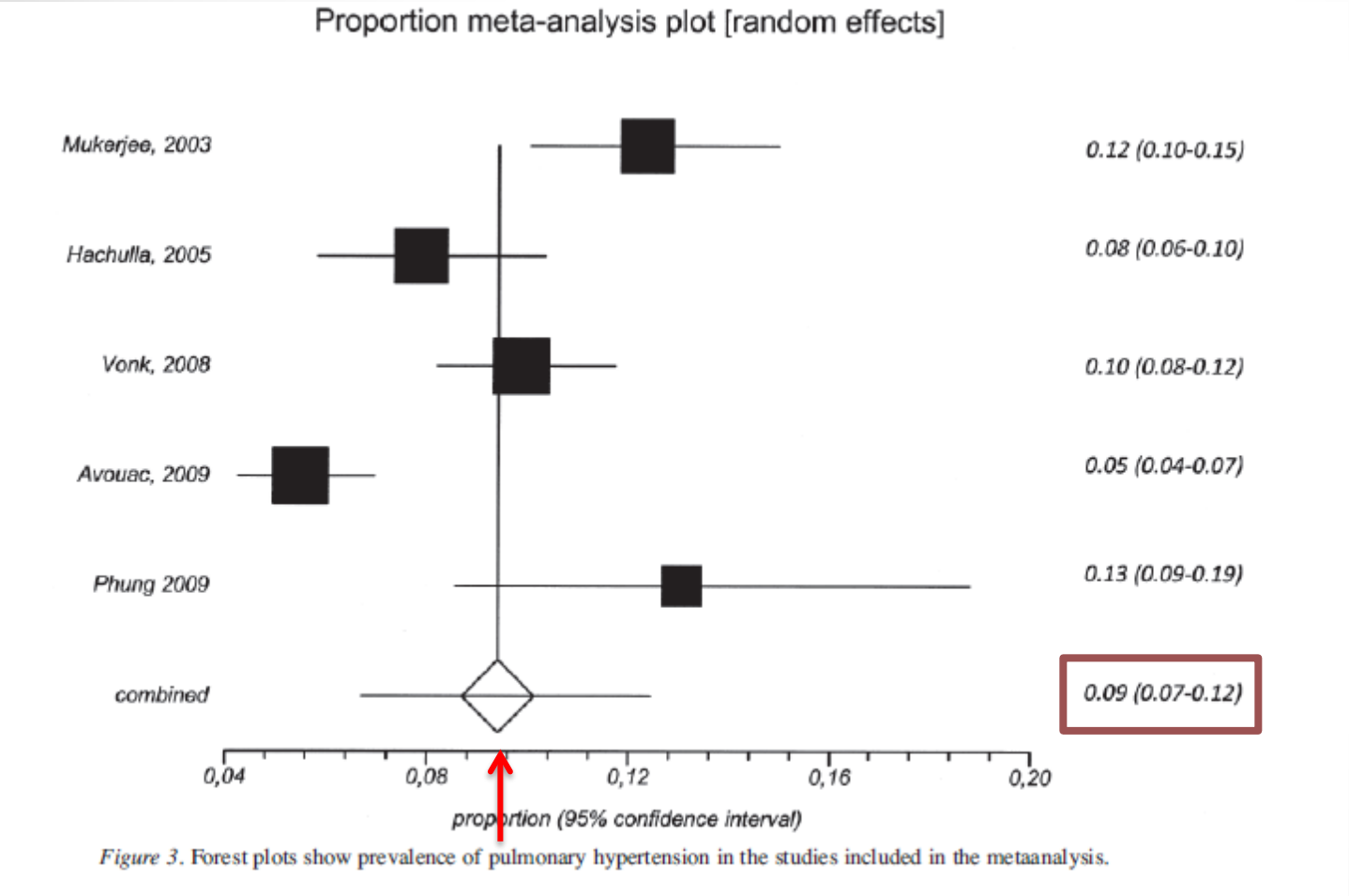


Figure 3. Forest plots show prevalence of pulmonary hypertension in the studies included in the metaanalysis.

3818 patients

- RHC-defined PAH
- 58 ±14 years
- 82 % women
- SSc duration 9±8 years

Avouac et al., 2009

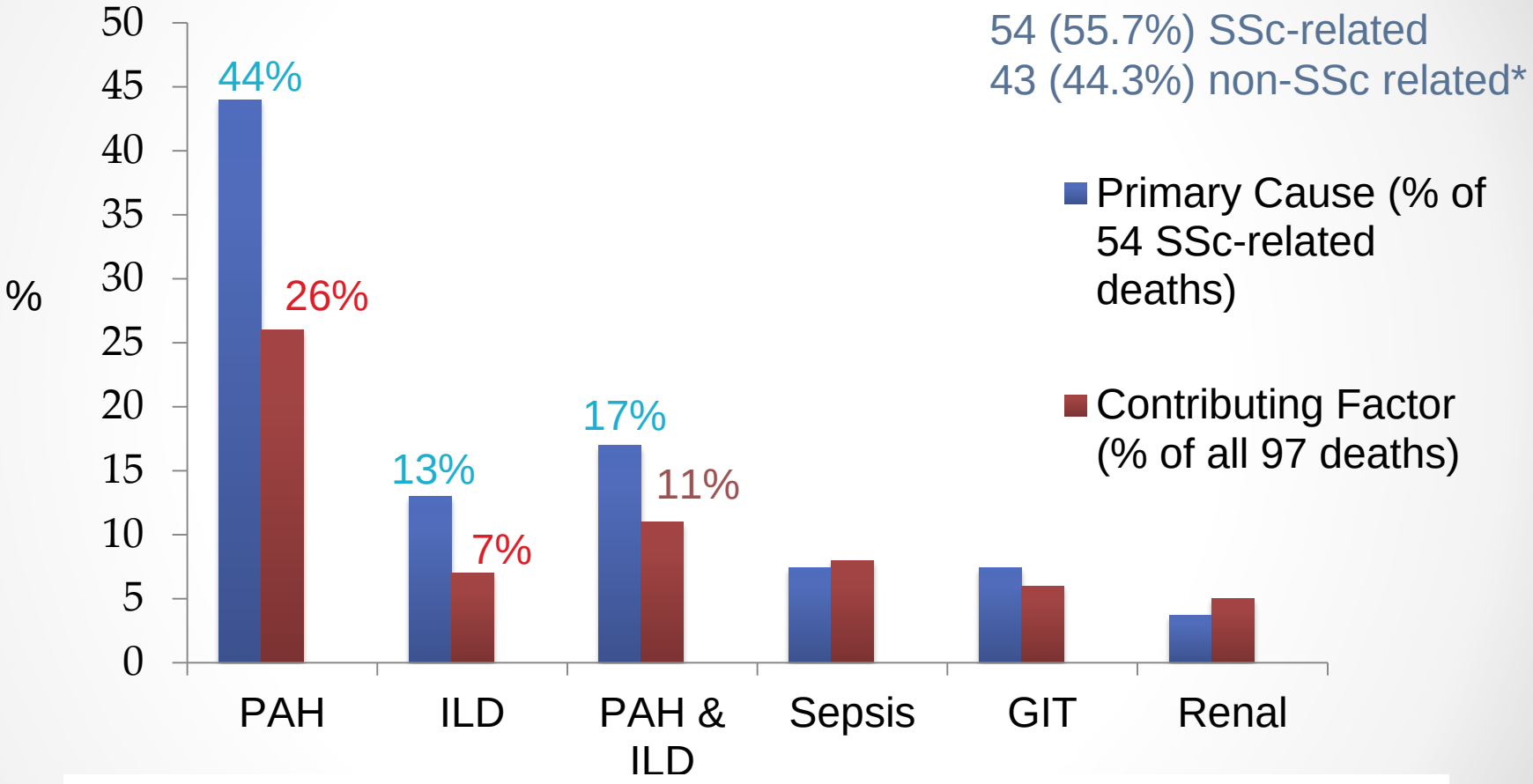
Characteristics of patients in the ASCS[1] (n=1,186)

	Limited n = 858 (67%) mean ± SD or %	Diffuse n = 328 (25%) mean ± SD or %	*P*
Age at recruitment, years	62.4 (±12.4)	58.1 (±13.1)	< .001
Female	90.7%	76.8%	< .001
Disease duration at recruitment, years	12.1 (±10.3)	9.3 (±9.1)	< .001
Auto-antibodies centromere	59.15%	10.20%	< .001
Scl 70 +ve	8.34%	31.25%	< .001
RNA polymerase III	4.52%	35.26%	< .001
ILD (HRCT scan)	21.33%	40.85%	< .001
PAH (RHC)	13.29%	9.45%	n.s.
Digital ulcers	23.83%	43.99%	< .001
Joint contractures	24.97%	68.8%	< .001
Renal crisis	1.68%	10.09%	< .001
Gastro-oesophageal reflux	82%	85%	n.s.
Fecal incontinence	26%	20%	n.s.

HRCT, high resolution CT; RHC, right heart catheter.

[1]Australian Scleroderma Cohort Study

"Scleroderma lung disease" – leading cause of mortality (ASCS, n=1279, 97 deaths)



Cardiopulmonary manifestations: primary cause of 74% of deaths and contribute to 44% of all deaths regardless of primary cause.

*malignancy, atherosclerosis sepsis

Risk Factors for SSc-PAH

Increased risk

- Severe Raynaud's, duration > 8 yrs
- Severe digital tip ulceration
- Extensive telangiectasiae
- Reduced nailfold capillaries
- Anti-U3 RNP or nucleolar ANA
- DLCO % predicted <60%*
- Increased FVC/DLCO >1.6
- Oxygen desaturation with exercise
- Increased baseline NT-pro-BNP*#
- pericardial effusion
- RBBB
- Raised ESR, IgG

No increased risk

- Rodnan total skin score
- Frequency of GI involvement
- Frequency of pulmonary fibrosis
- Mean FVC
- Anti-centromere Ab?

None performs well in the individual patient

*Increased baseline NT-pro-BNP (HR 9.97) and DLCO/VA ratio < 60% in the absence of extensive ILD (HR 36.66) were predictors of PH over 3 years and were poor prognostic features

#Correlates with PVR and inversely with 6MWT

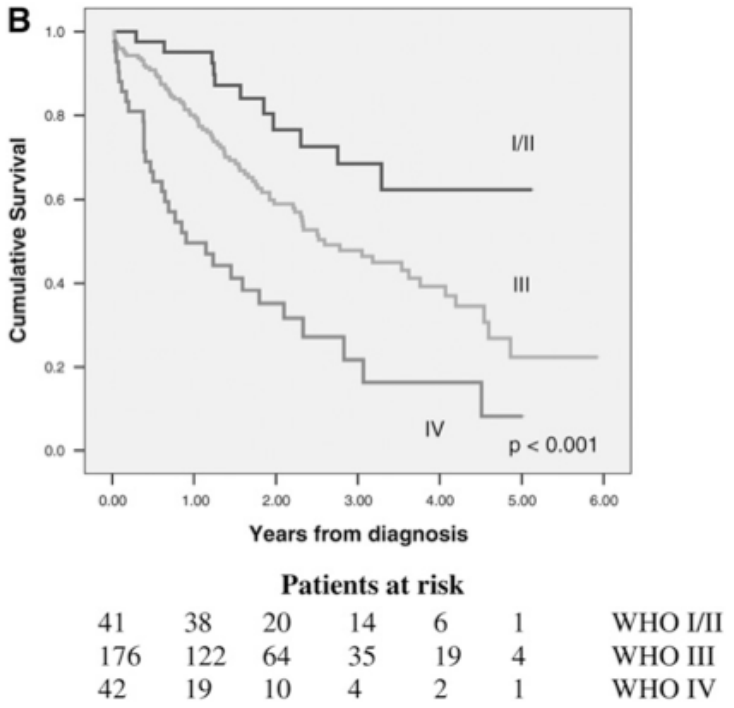
Steen VD Arthritis Rheum 2003;48:516; Hachullae et al.Arthritis Rheum 2005;52;3792; Chang et al J Rhematol 2006;33;269-274; Avouac J et al. J Rheumatol 2010; 37:2290; Allanore Y. et al. Arthritis Rheum. 2008;58:284; Williams MH et al. Eur Heart J 2006;27:1485; Mathias SC et al. Eur Resp J 2009

Barriers to earlier PAH detection

- PAH is clinically silent in the initial stages
- Reduced exercise capacity in later stages can be erroneously attributed to
  - Interstitial lung disease
  - Left heart disease
  - Musculoskeletal disease – muscle vasculopathy
  - Anemia
  - Physical de-conditioning
- Ongoing adaptation to disease and denial
- Reluctance to perform RHC

A detailed history is essential for detecting early changes in exercise capacity in order to identify PAH early

Rationale for screening: Less severe functional classes have better survival



The UK CTD-PAH registry

Lead time bias or are patients seen too late in tertiary centres and strategies for earlier detection are needed?

Condliffe R et al. Am J Resp Crit Care Med 2009;179:151-7

‘EARLY’ study: 14% in WHO class II declined by 6 months with no treatment

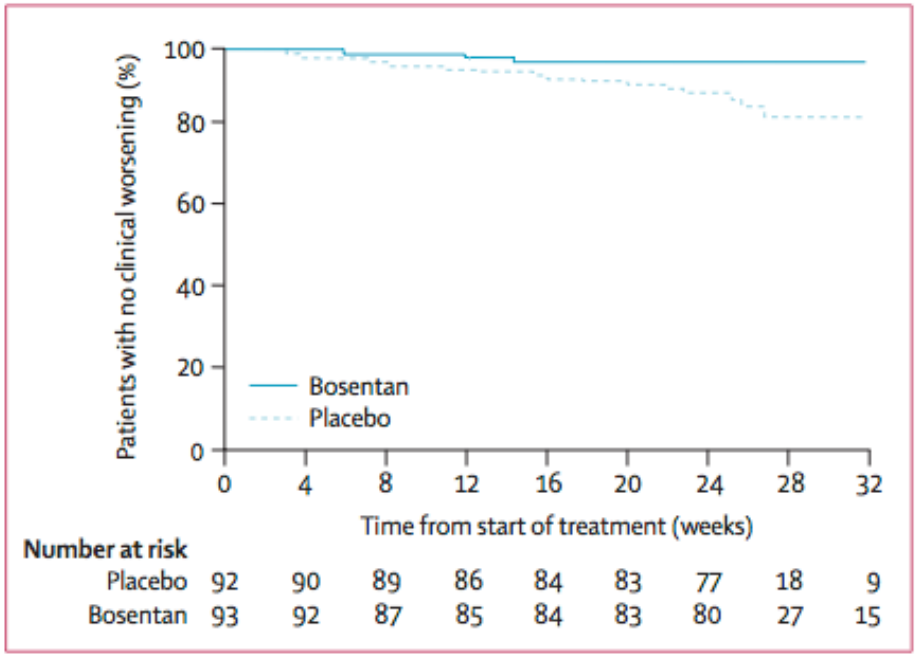
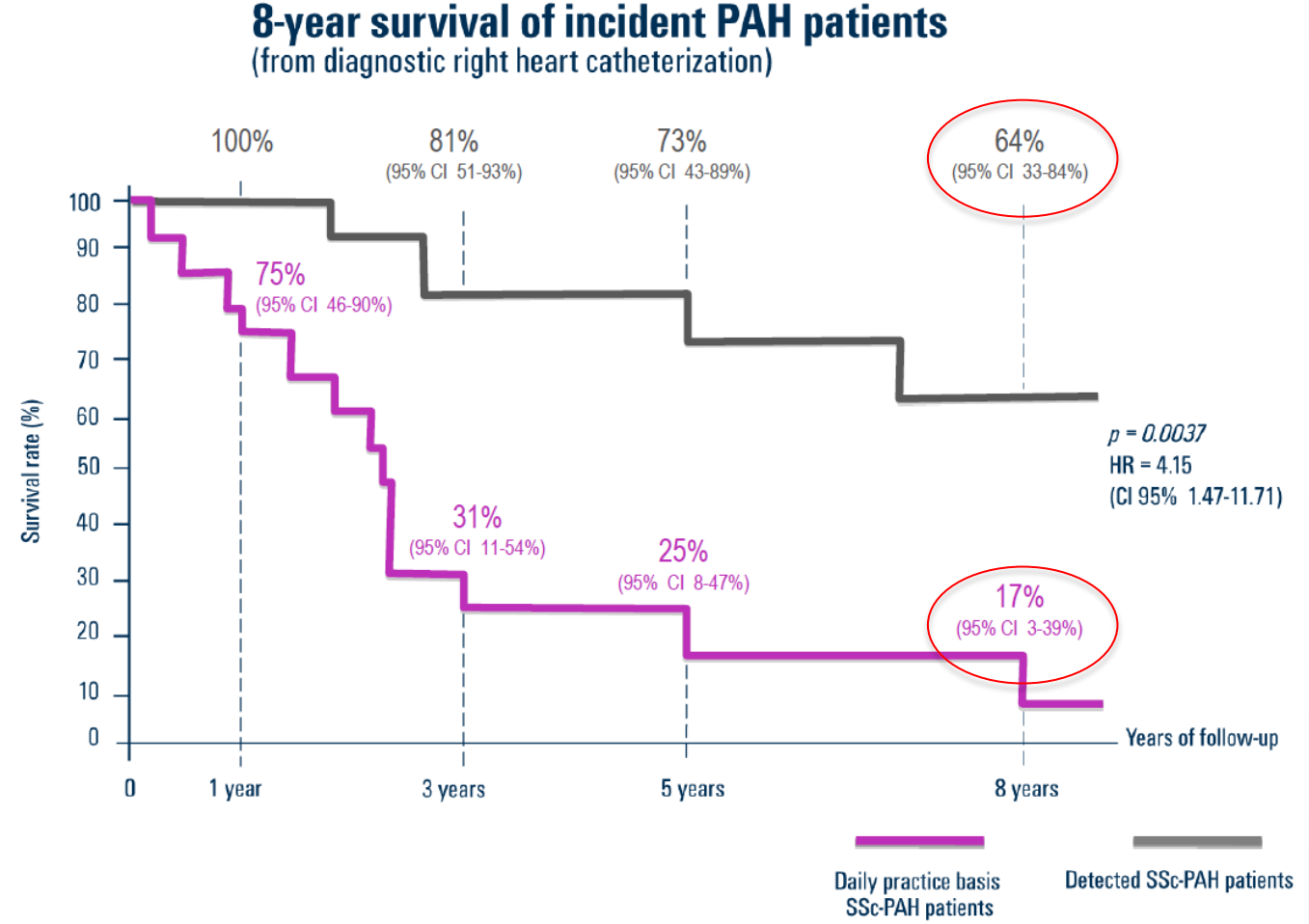


Figure 4: **Time to clinical worsening**

Galie et al, Lancet 2008

SSc-PAH screening programs can reduce mortality



Screening

No Screening

Humbert, Arthritis and Rheumatism, 2011

Screening for PAH

- RHC ('gold standard') is required for definitive diagnosis of PAH
  - BUT, not feasible for screening (invasive)

- Current international guidelines* recommend annual transthoracic echocardiography (echo) ± pulmonary function tests (PFT) as the 'first tier' screen
  - Limitations of echo:
    - Pulmonary artery pressure cannot be estimated in up to 39% of patients due to an absent TR jet[1,2,3]
    - poor image quality
    - significant cost
    - requirement for specific expertise

**ESC/ERS, 2009; ACCF/AHA, 2009; PAH centres of UK, 2003*

[1]Denton, 1997; [2]Mathai, 2011; [3]Coghlan, 2013

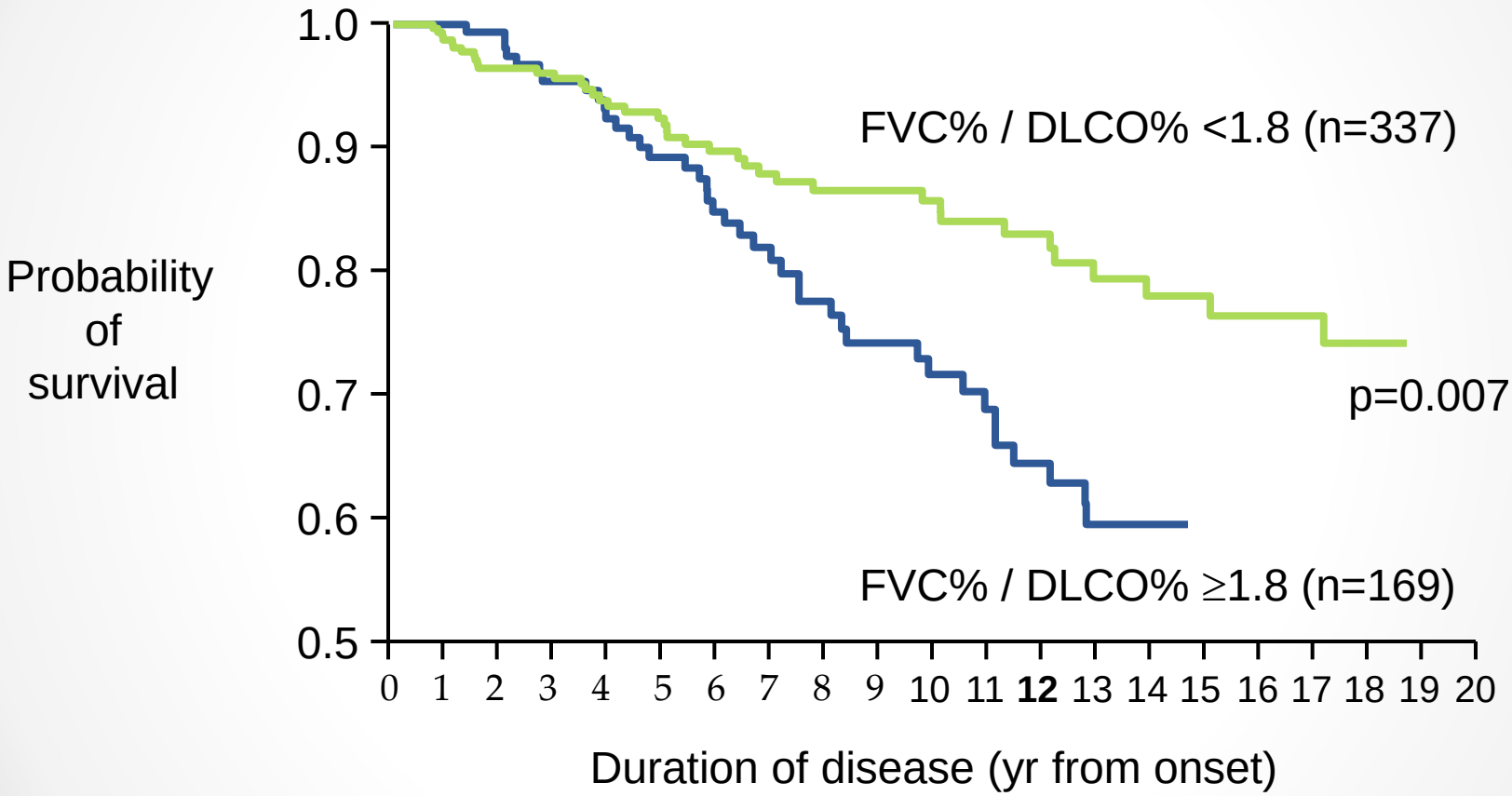
Screening Guidelines for PAH – rely on ECHO

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm.	

ESC/ERS Guidelines,
Galie et al. European Heart Journal 2015

Ratio of FVC % to DLCO % is related to survival in SSc



Disproportionate and/or isolated reduction in gas exchange (diffusing capacity) is dominant determinant of survival in all forms of SSc lung.

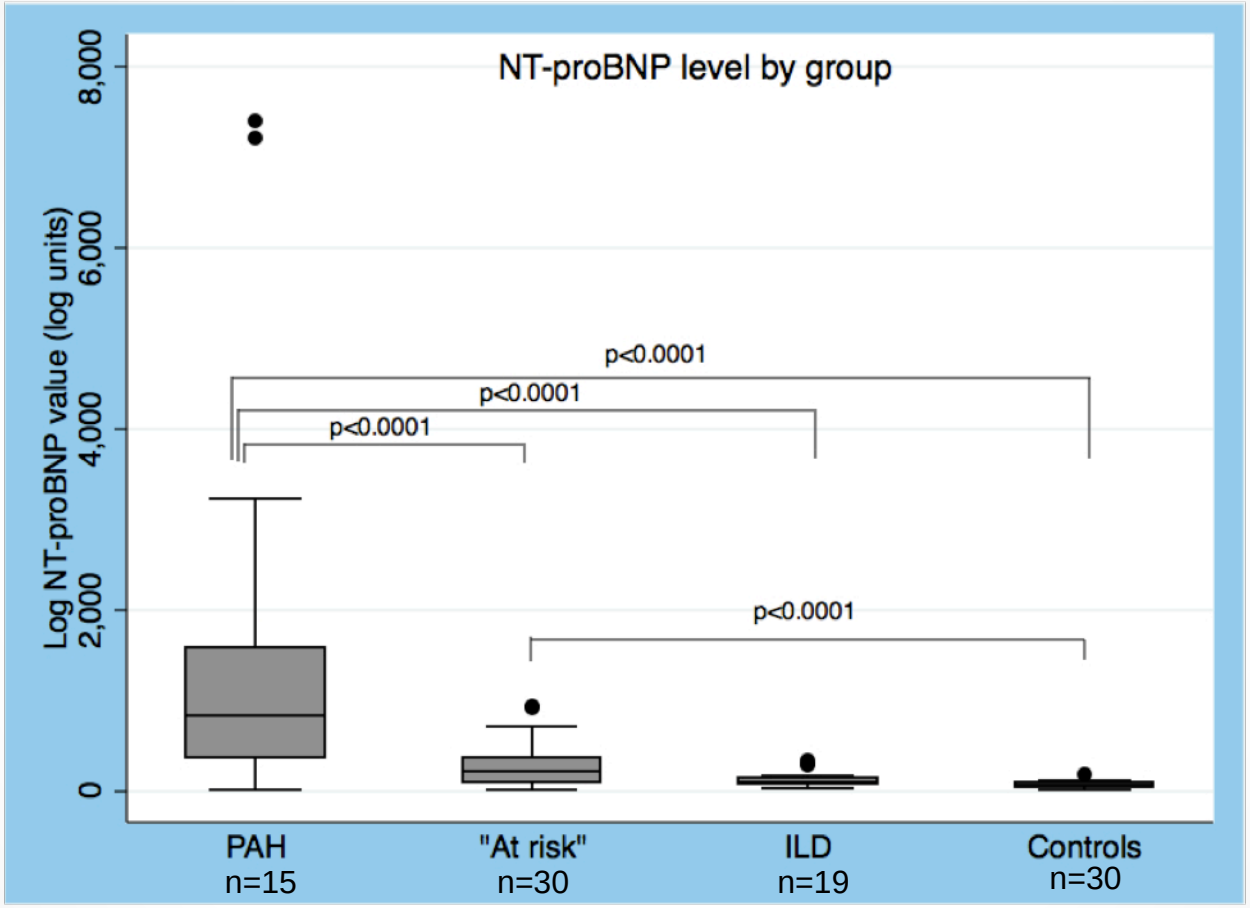
Seibold JR et al. J Rheumatol 2006;33.

NT-pro Brain Natriuretic Peptide (NT-proBNP)

- NT-pro BNP has emerged as a candidate biomarker for SSc-PAH
- 76 AA polypeptide released from cardiac myocytes in response to ventricular wall stress
  - Simple blood test
  - Renally excreted; levels are validated in those with eGFR≥30ml/min
  - PBS reimbursed for use in ED to investigate SOB (cardiac v. respiratory)
- Measured by Elecsys proBNP II sandwich immunoassay (Roche diagnostics) with a range from 5 - 35,000pg/ml

Mukerjee, 2003; Williams 2005; Allanore 2009

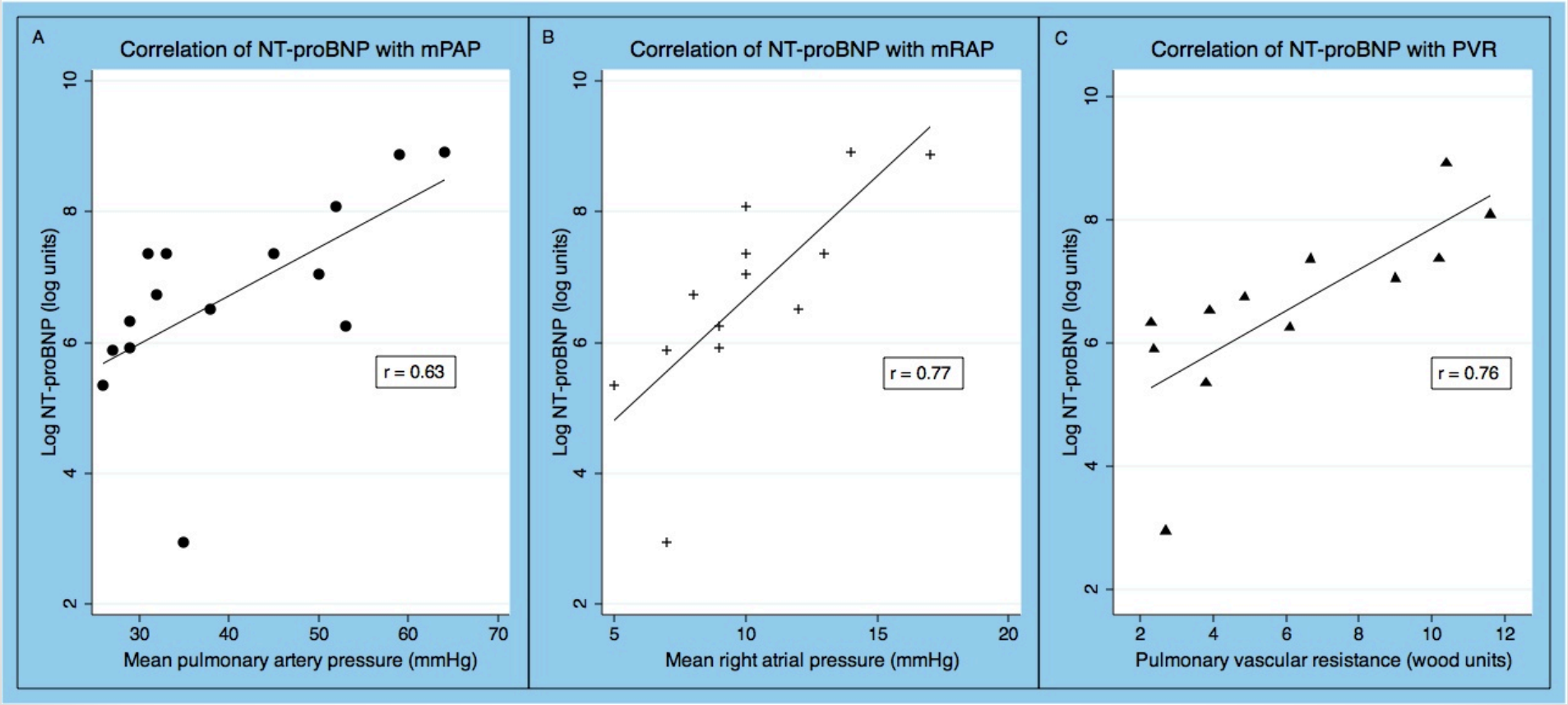
Significantly higher NT-proBNP in SSc-PAH



"At risk": Echo sPAP > 36mmHg (37-49mmHg) and either DLCO < 50% or FVC/DLCO ≥ 1.6

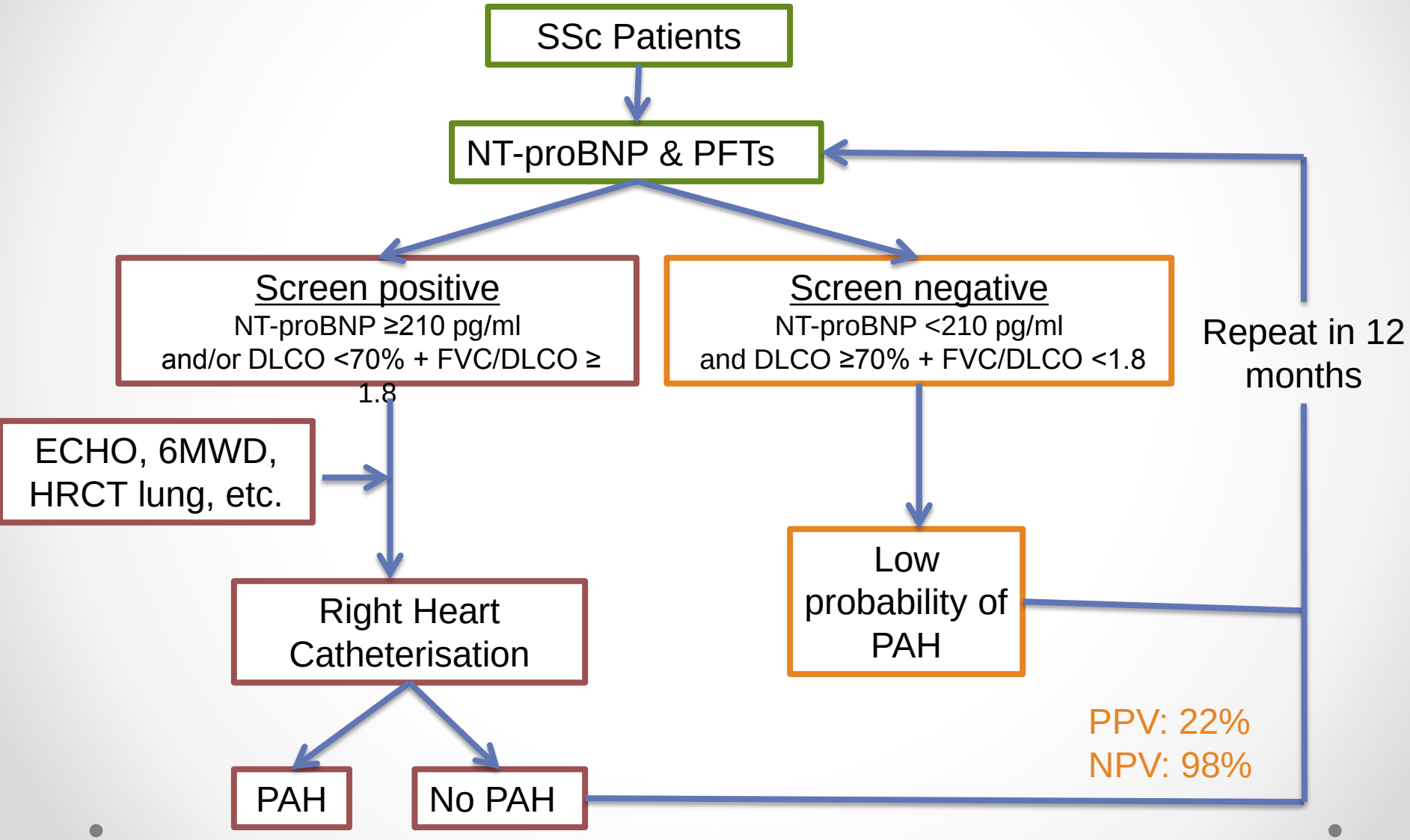
Thakkar et al. Arthritis Research & Therapy 2012.

NT-proBNP correlates with haemodynamics at RHC



- *Thakkar et al. Arthritis Research & Therapy 2012.*

Proposed Screening Algorithm ($ASIG_{Proposed}$)

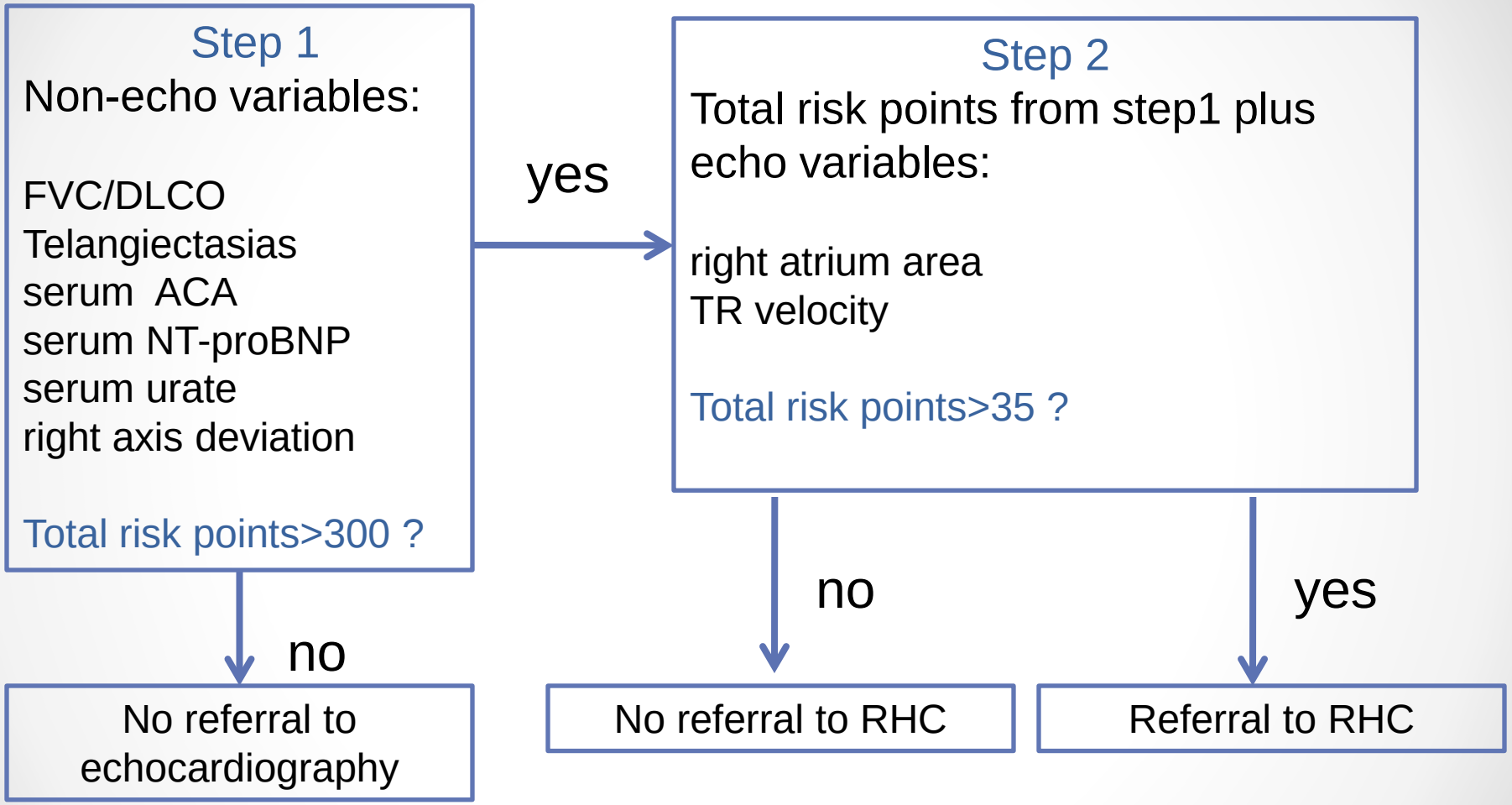


Thakkar et al., Arthritis Res Ther June 2012; Nov 2013

A Comparison of the Predictive Accuracy of Three Screening Models (DETECT v. ESC/ERS v. $ASIG_{NEW}$) for Pulmonary Arterial Hypertension in Systemic Sclerosis

YJ Hao, V Thakkar, W Stevens, D Prior, C Rabusa, P Youssef, E Gabbay , J Roddy, J Walker, J Zochling, J Sahhar, P Nash, S Lester, C Hill, M Rischmueller, S Proudman, and M Nikpour.

DETECT decision tree

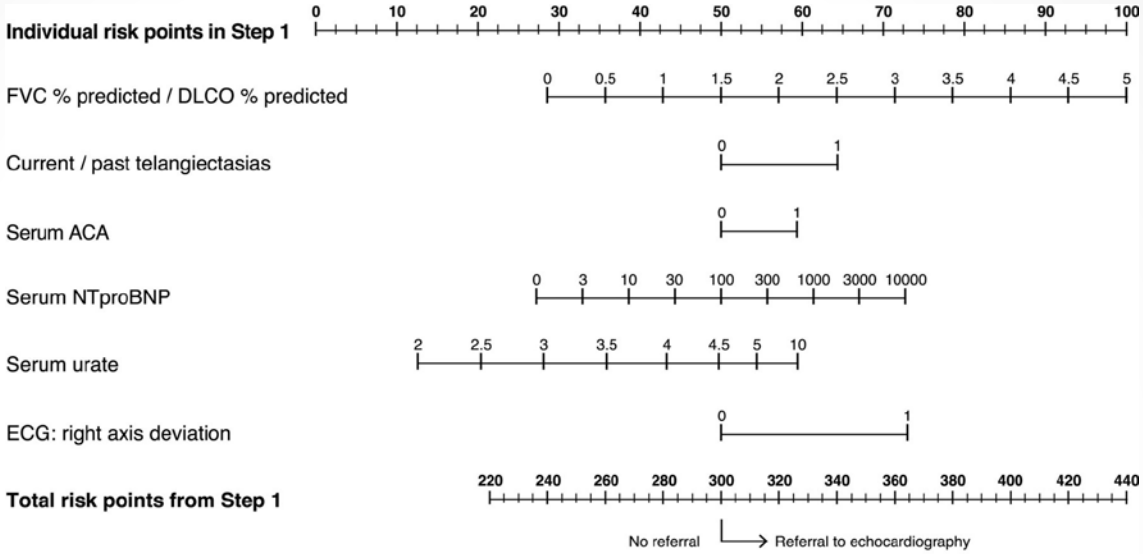


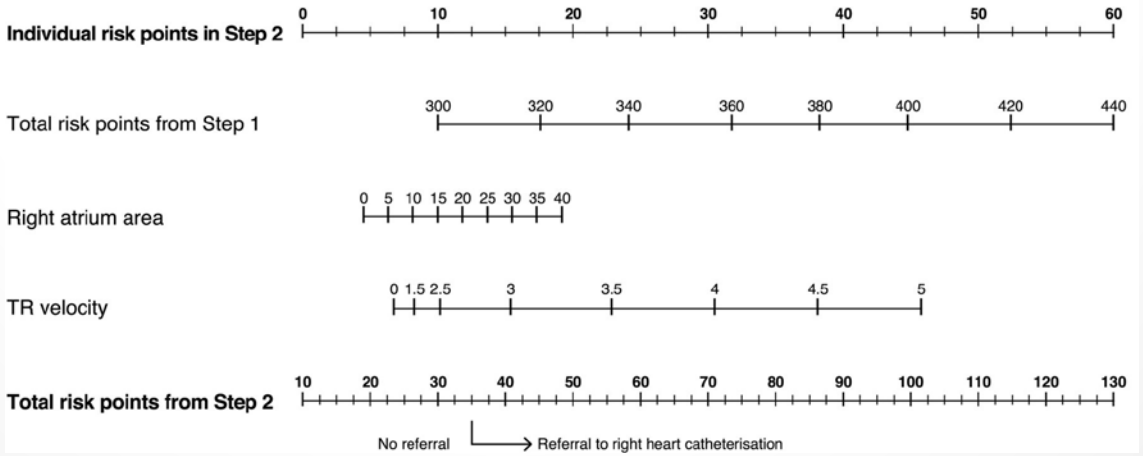
A novel screening model for SSc-PAH developed from a world-wide multi-centre cross-sectional study.

- Inclusion: DLCO<60%; Exclusion: FVC<40%

Coghlan J G et al. Ann Rheum Dis, 2013

Nomograms for applying the DETECT algorithm: determining the likelihood of PAH and cut-off points for referring a patient for ECHO (Step 1) and subsequent RHC (Step 2).





Coghlan J G et al. Ann Rheum Dis, 2013

ARD

DETECT

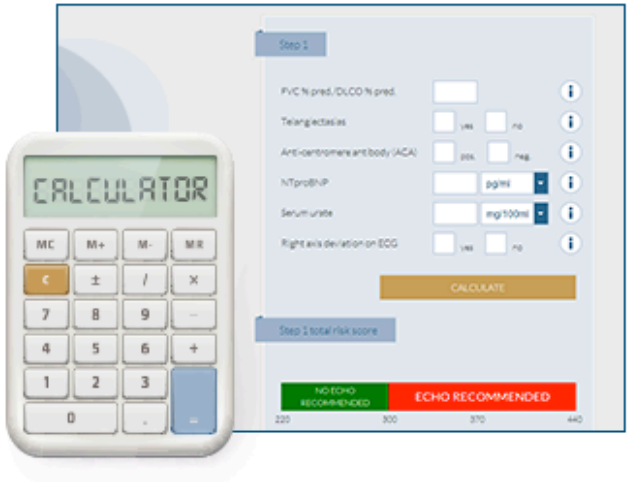
DETECTion of PAH in SSc

HOME | WHAT IS DETECT? | PAH RISK CALCULATOR | ABOUT SSC AND PAH | SUPPORTING INFORMATION

WELCOME TO THE PAH RISK CALCULATOR

The PAH risk calculator is a tool for all physicians dealing with systemic sclerosis (SSc). The calculator was developed and validated in the DETECT study. The DETECT study was designed and carried out by a group of experts, all of whom are physicians practising in different countries, and was supported by Actelion Pharmaceuticals Ltd.

The calculator was developed for your daily clinical practice. It will help you to identify and diagnose SSc patients with pulmonary arterial hypertension (PAH), which is a serious condition that develops in 8-13% of SSc patients and is the leading cause of death in patients with this disease. The calculator is based on an algorithm with a high sensitivity and specificity and can help you to decide which of your SSc patients should be evaluated using echocardiography, and of those patients who should be referred for right heart catheterization.



START CALCULATOR

Comparison of the predictive accuracy of three models for screening for SSc-PAH

- 73 consecutive SSc patients with suspected PAH undergoing RHC*:
  - 34 (47%) no PH
  - 39 (53%) PH
    - 27 (37%) WHO group1 PH (PAH)
    - 4 (6%) WHO group 2 PH
    - 8 (10%) WHO group 3 PH
- 3 patients with undetectable TRV were excluded from evaluating ESC/ERS guidelines.

*excluded patients with FVC<40%. No exclusion based on DLCO

Comparison of the predictive accuracy of three models for screening for SSc-PAH

	DETECT n=61	ESC/ERS n=58	$ASIG_{NEW}$ n=61
Sensitivity (95% CI)	100% (87.2-100)	96.3% (81-99.9)	100% (87.2-100)
Specificity (95% CI)	35.3% (19.7-53.5)	29.0% (19.7-53.3)	47.1% (29.8-64.9)
PPV (95% CI)	55.1% (40.2-69.3)	54.2% (39.2-68.6)	60% (44.3-74.3)
NPV (95% CI)	100% (63.1-100)	90.0% (55.5-99.7)	100% (79.4-100)
Referral rate for RHC	**80%**	**81%**	**68%**

Comparison of the predictive accuracy of three models for screening for SSc-PAH

- The specificity of all models is low, as expected for a screening test.

- $ASIG_{NEW}$ algorithm has the highest specificity and lowest referral rate for RHC.
  - DETECT would have missed 4 PAH if limited to DLCO<60%

- Unlike ESC/ERS and DETECT, the $ASIG_{NEW}$ algorithm does not rely on TRV and can be applied to patients with undetectable TR

Cost Savings with a Biomarker-Based Screening Algorithm for SSc-PAH ($ASIG_{NEW}$)

	$ASIG_{OLD}$	$ASIG_{NEW}$
Total number of patients	643	643
Number (%) screen+	256 (40%)	231 (36%)
% screen+ with PAH on RHC	45%	50%
TTE performed	643	231
RHC performed	256	231
NNS to get one screen+	2.5	2.78
Number of RHC to diagnose one case PAH	2.2	2.0
NNS to diagnose one case of PAH	5.5	5.56
Total cost of screening and diagnosis	$851,917	$727,833
Cost of diagnosis of one case of PAH	$7,311.70	$6,300.20

NNS=number needed to screen. All costs are in Australian Dollars.

Proposed Screening Algorithm ($ASIG_{Proposed}$)

In the first year of screening, the proposed screening algorithm results in:

- 64% reduction in the number of echocardiograms
- 10% reduction in number of RHC
- 1-5 cases of PAH that would have been missed with 'old' algorithm
- Need to do 2 RHC to diagnose one case of PAH
- Total screening (and RHC) cost saving of $946,000.00 in the first year and $851,400 for each subsequent year for entire Australian SSc patients per year
- A cost saving of $1,936.00 (15%) per case of PAH diagnosed

Coupled with ease and accessibility of NT-proBNP testing, makes a compelling case for listing this test on the Medicare Benefits Schedule for reimbursement in screening for SSc-PAH.

PAH-specific therapies

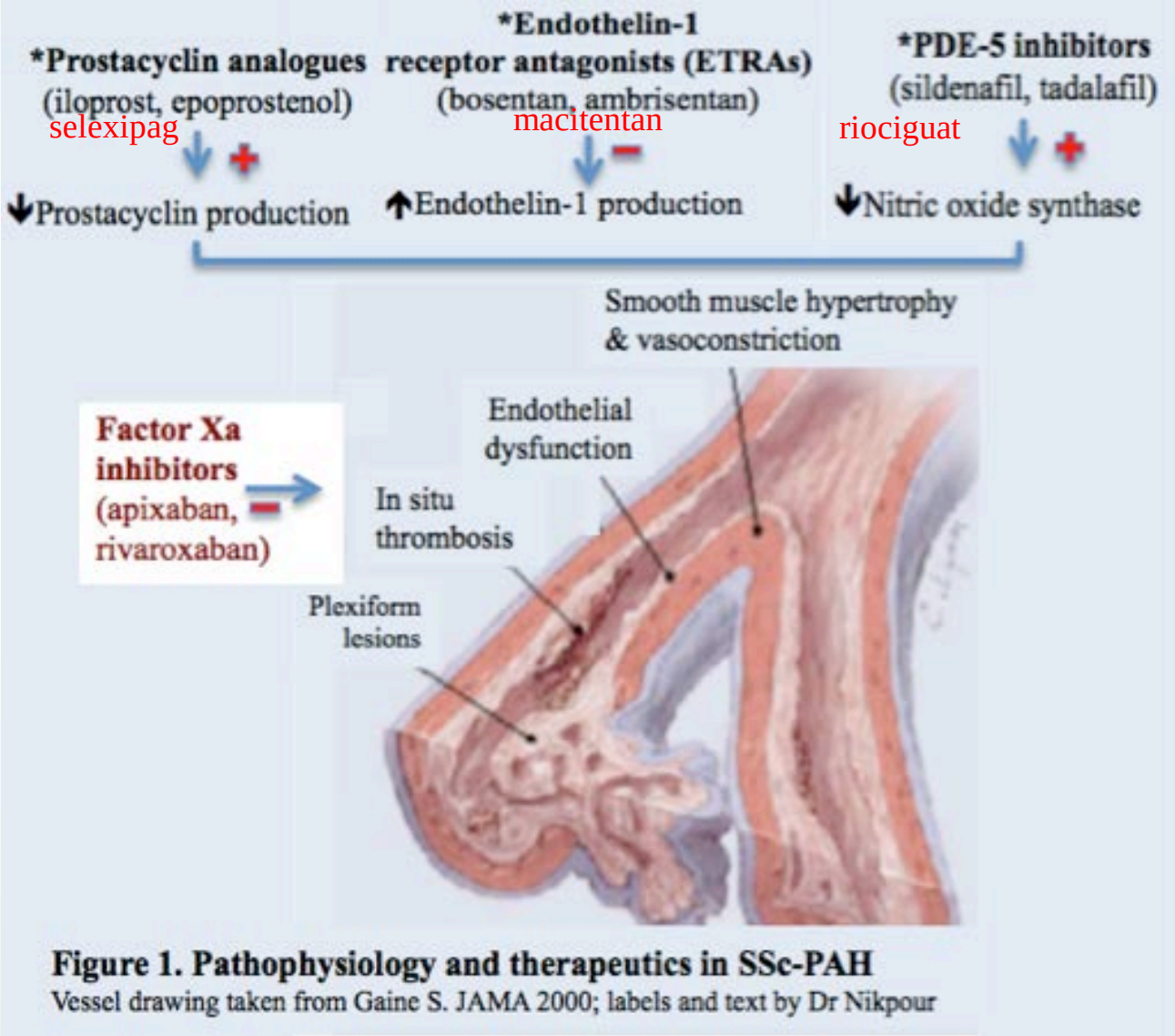
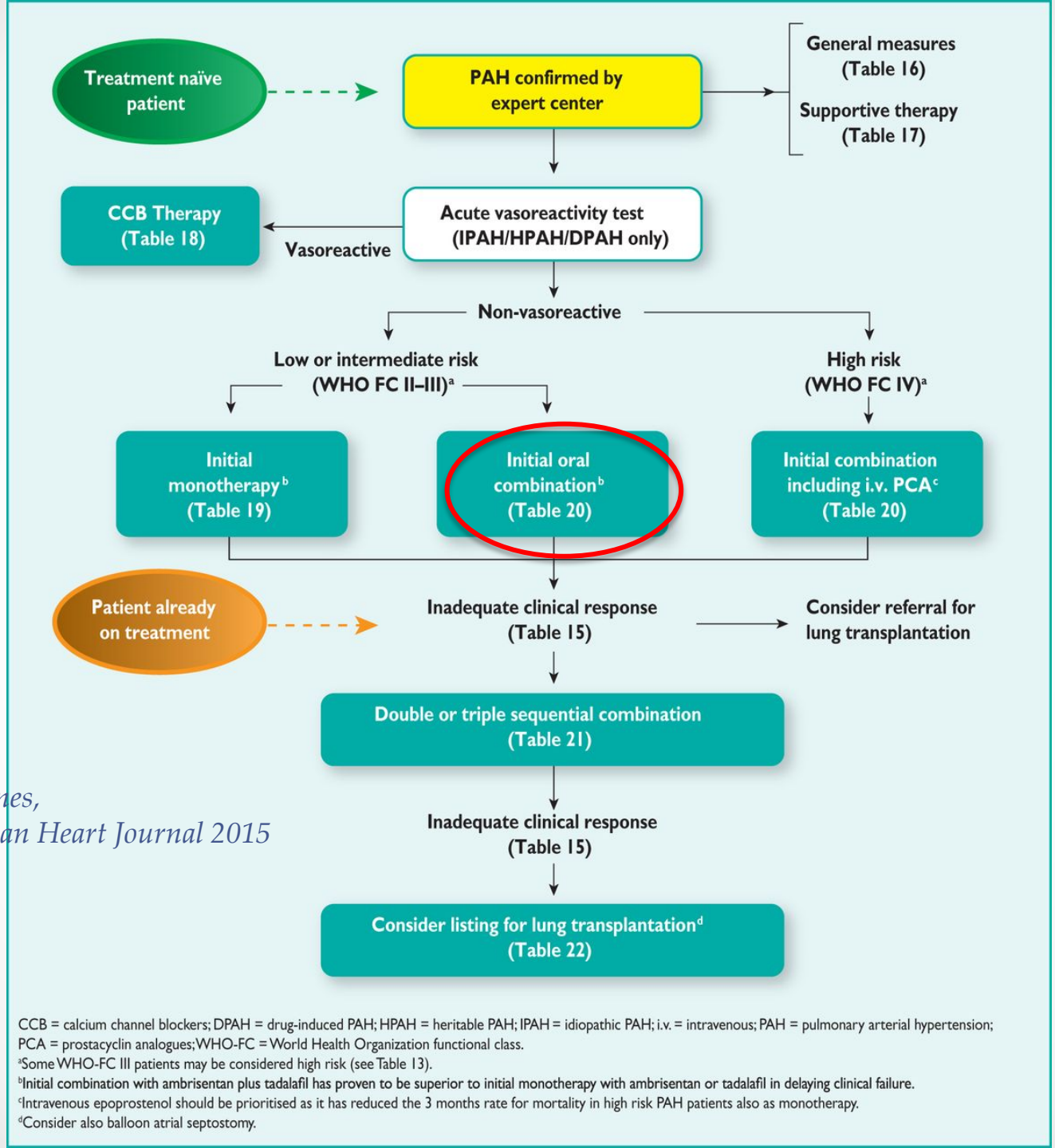


Figure 1. Pathophysiology and therapeutics in SSc-PAH

Vessel drawing taken from Gaine S. JAMA 2000; labels and text by Dr Nikpour



CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; i.v. = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health Organization functional class.

[a]Some WHO-FC III patients may be considered high risk (see Table 13).

[b]Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.

[c]Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.

[d]Consider also balloon atrial septostomy.

ESC/ERS Guidelines,
Galie et al. European Heart Journal 2015

Table 20 Recommendations for efficacy of initial drug combination therapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. Sequence is by rating

Measure/ treatment	Class[a]-Level[b]						Ref.[c]
	WHO-FC II		WHO-FC III		WHO-FC IV		
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C	247
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C	-
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C	246
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C	198, 245
Other ERA or PDE-5i + s.c. treprostinil			IIb	C	IIb	C	-
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C	IIb	C	-

ESC/ERS Guidelines,
Galie et al. European Heart Journal 2015

Combination therapy

- Targets the multiple pathobiologic mechanisms present in PAH

- No long term data available
  - 6 RCTs with heterogeneous results
  - Benefit in meta -analysis

- Australian experience
  - In SSc-PAH patients on dual therapy, 1-year survival 72% and 2-year survival 48%

Keogh A et al. Intern Med J 2011;41(3)235.

  - In Australia, patient funded or obtained on compassionate grounds.

Stratifying Prognosis in PH

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

ESC/ERS Guidelines,
Galie et al. European Heart Journal 2015

Table 16 Recommendations for general measures

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that PAH patients avoid pregnancy	I	C	160, 161
Immunization of PAH patients against influenza and pneumococcal infection is recommended	I	C	
Psychosocial support is recommended in PAH patients	I	C	168
Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy	IIa	B	153–157
In-flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently <8 kPa (60 mmHg)	IIa	C	
In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible	IIa	C	
Excessive physical activity that leads to distressing symptoms is not recommended in PAH patients	III	C	

ESC/ERS Guidelines,
Galie et al. European Heart Journal 2015

Table 17 Recommendations for supportive therapy

Recommendations	Class[a]	Level[b]	Ref.[c]
Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention	I	C	178
Continuous long-term O_2 therapy is recommended in PAH patients when arterial blood O_2 pressure is consistently <8 kPa (60 mmHg)[d]	I	C	179
Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of anorexigens	IIb	C	84,171, 175–177
Correction of anaemia and/or iron status may be considered in PAH patients	IIb	C	184
The use of angiotensin-converting enzyme inhibitors, angiotensin-2 receptor antagonists, beta-blockers and ivabradine is not recommended in patients with PAH unless required by co-morbidities (i.e. high blood pressure, coronary artery disease or left heart failure)	III	C	

ESC/ERS Guidelines,
Galie et al. European Heart Journal 2015

Real-life studies of SSc-PAH – 3 year survival is still poor

	1-year	2-year	3-year
ASCS* (CTD-PAH)	94%	89%	73%
Williams *et al.* (SSc-PAH)	81%	71%	
Condliffe *et al.* (SSc-PAH)	78%	58%	47%
Chung *et al.* (CTD-PAH)	86%		

*Royal Perth Hospital, RAH, FMC, TQEH, St Vincent's Hospital Melbourne and Monash Medical Centre

Lefevre, 2013; Condliffe R et al. Am J Resp Crit Care Med 2009;179:151-7; Chung L 2010

Optimising the treatment of SSc-PAH

Beyond the advanced PAH-specific therapies

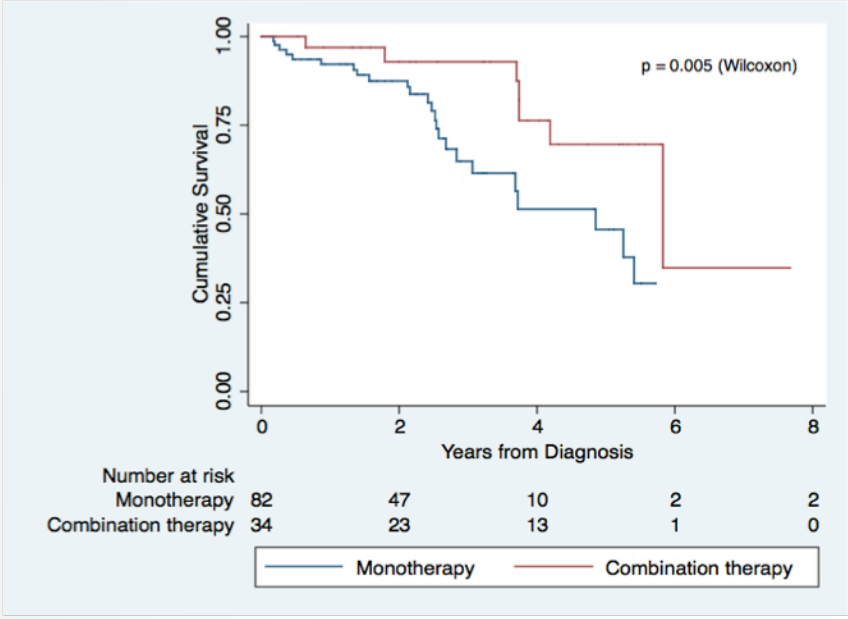
Survival and Predictors of Mortality in Australian Patients with Connective Tissue Disease-Associated Pulmonary Arterial Hypertension

Gene-Siew Ngian, Wendy Stevens, David Prior, Janet Roddy, Eli Gabbay, Ai Tran, Jillian Byron, Robert Minson, Catherine Hill, Joanne Sahhar, Ken Chow, Susanna Proudman and Mandana Nikpour.

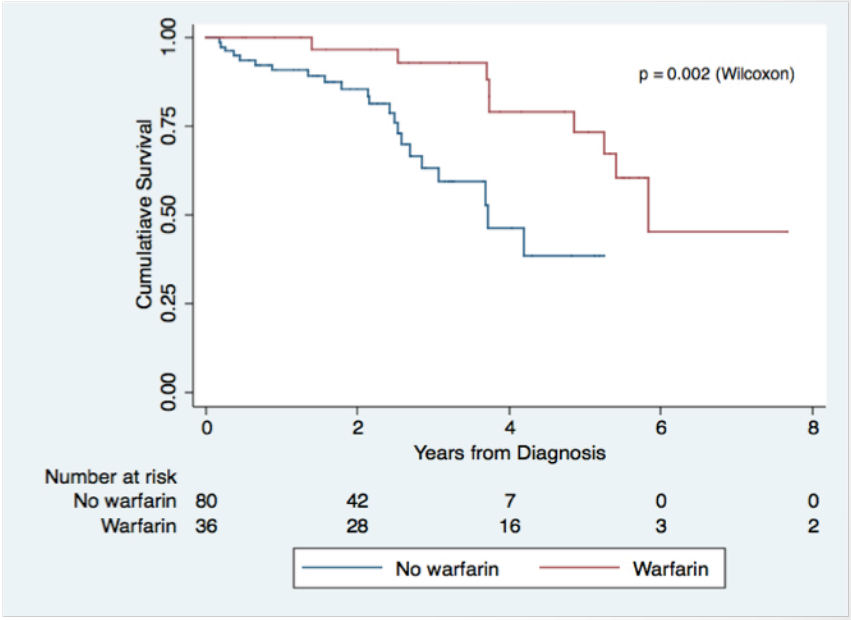
Arthritis Research & Therapy 2012 14:R213.

Australian patients with SSc=PAH, 2000-2007

Combination therapy significantly improved survival



Anticoagulation significantly improved survival



36 (31%) patients on warfarin for PAH at physician discretion

*Royal Perth Hospital, RAH, FMC, TQEH, St Vincent's Hospital Melbourne and Monash Medical Centre

Ngian et al., Arthritis Res Ther. 2012 Oct 5;14(5):R213

Mortality – multivariable analysis

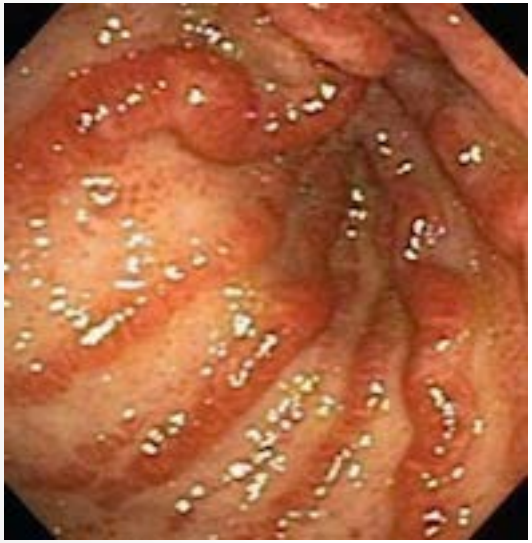
Variable	Multivariate HR (95%CI)	P value
Male sex	2.1 (0.4 – 10.0)	0.37
WHO class at baseline	3.5 (1.3 – 9.4)	0.01
ILD	2.3 (0.8 – 6.3)	0.11
mRAP at baseline	1.1 (1.0 – 1.2)	0.03
Baseline 6MWD	0.995 (0.991 – 0.999)	0.03
Pericardial effusion	3.5 (1.1 – 11.1)	0.04
Warfarin therapy	0.2 (0.1 – 0.8)	0.03
Combination therapy*	0.2 (0.0 – 0.8)	0.03

*Most common combination was bosentan and sildenafil

Warfarin associated with improved survival independently of baseline PAH severity

	Yes N (%) or mean±sd (n=36)	No N (%) or mean±sd (n=81)	P value
Male	2 (5.6%)	10 (12.4%)	0.26
Age at CTD Dx	48.5 ± 14.3	51.1 ± 14.7	0.46
Age at PAH Dx	59.7 ± 13.1	62.5 ± 10.6	0.23
Antiphospholipid Ab	8 (22.1%)	19 (23.5%)	0.74
Pericardial effusion	9 (25.0%)	5 (6.2%)	0.004
Baseline 6MWD, m	286 ± 116	340 ± 128	0.06
Baseline mPAP, mmHg	42.0 ± 11.5	33.4 ± 12.0	0.001
Baseline mRAP, mmHg	7.1 ± 4.3	6.9 ± 4.1	0.85

No identifiable contraindication to anticoagulation in 69% patients not on warfarin, indicating physician uncertainty re role of anticoagulation in this setting. No site-specific trends observed.



Gastric Antral Vascular Ectasia (GAVE: 'watermelon stomach')

Occurs in <5% patients with SSc but associated with PAH

Cause of recurrent iron deficiency anemia

Detected on endoscopy

Recurrent bleeding from GAVE is a contraindication to anticoagulation

SSc patients can have other GI vascular lesions that might bleed with anticoagulation

Correlates of APLA in SSc

Variable*	ACA type	Odds ratio	95% CI	*p* value
PAH	ACA-IgG +	1.70	1.01-2.93	0.047
	ACA-IgG >40	4.60	1.02-20.8	0.047
ILD	ACA-IgM +	2.04	1.40-3.00	<0.0001
	ACA-IgG	1.84	1.20 -2.80	0.005
	ACA-IgM >20	2.36	1.17-4.76	0.016
	ACA-IgG +	1.84	1.20-2.83	0.005
	ACA-IgG >20	2.15	1.03-4.50	0.041
ILD-PH	ACA-IgG +	2.10	1.05-4.20	0.036
Digital ulcers	ACA-IgG +	1.76	1.16-2.67	0.008
Raynaud's	ACA-IgM +	2.39	1.08-5.27	0.031

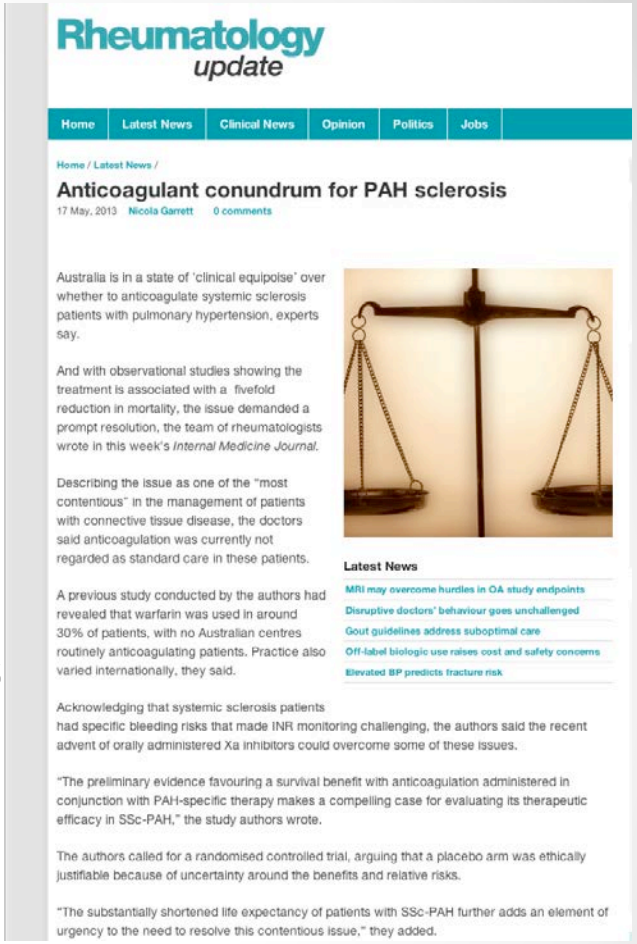
One or more types of APLA were present in 226 (24.0%) of 940 patients included in the study.

Morrisroe K et al., Clin Exp Rheumatol 2014

Viewpoint
Should patients with scleroderma-related pulmonary arterial hypertension be anticoagulated?

M. Nikpour, W. Stevens, S. Proudman,
R. Buchbinder, D. Prior, J. Zochling, T. Williams
E. Gabbay, H. Nandurkar

Intern Med J. 2013 May;43(5):599-603.



Rheumatology update

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Anticoagulant conundrum for PAH sclerosis

17 May, 2013 Nicola Garrett 0 comments

Australia is in a state of 'clinical equipoise' over whether to anticoagulate systemic sclerosis patients with pulmonary hypertension, experts say.

And with observational studies showing the treatment is associated with a fivefold reduction in mortality, the issue demanded a prompt resolution, the team of rheumatologists wrote in this week's *Internal Medicine Journal*.

Describing the issue as one of the "most contentious" in the management of patients with connective tissue disease, the doctors said anticoagulation was currently not regarded as standard care in these patients.

A previous study conducted by the authors had revealed that warfarin was used in around 30% of patients, with no Australian centres routinely anticoagulating patients. Practice also varied internationally, they said.

Latest News

MRI may overcome hurdles in OA study endpoints

Disruptive doctors' behaviour goes unchallenged

Gout guidelines address suboptimal care

Off-label biologic use raises cost and safety concerns

Elevated BP predicts fracture risk

Acknowledging that systemic sclerosis patients had specific bleeding risks that made INR monitoring challenging, the authors said the recent advent of orally administered Xa inhibitors could overcome some of these issues.

"The preliminary evidence favouring a survival benefit with anticoagulation administered in conjunction with PAH-specific therapy makes a compelling case for evaluating its therapeutic efficacy in SSc-PAH," the study authors wrote.

The authors called for a randomised controlled trial, arguing that a placebo arm was ethically justifiable because of uncertainty around the benefits and relative risks.

"The substantially shortened life expectancy of patients with SSc-PAH further adds an element of urgency to the need to resolve this contentious issue," they added.

Canadian Journal of Cardiology 30 (2014) 879–887

Systematic Review/Meta-analysis

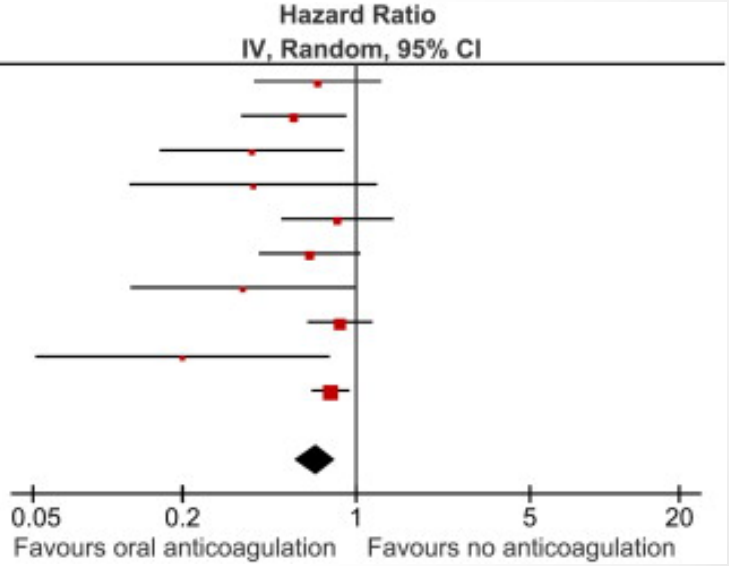
Oral Anticoagulation for Pulmonary Arterial Hypertension: Systematic Review and Meta-analysis

Daniel Caldeira, MD,[a,b,c] Maria José Loureiro, MD,[c] João Costa, MD, PhD,[a,b,d,e] Fausto J. Pinto, MD, PhD,[f] and Joaquim J. Ferreira, MD, PhD[a,b]

Study	Weight	OA Total	Control Total	Hazard Ratio IV, Random, 95% CI	Year
Storstein	7.8%	10	7	0.70 [0.39, 1.26]	1966
Fuster	10.6%	78	37	0.56 [0.34, 0.91]	1984
Rich	4.2%	35	29	0.38 [0.16, 0.89]	1992
Ogata	2.4%	7	13	0.39 [0.12, 1.21]	1993
Frank (PPH)	9.6%	24	45	0.84 [0.50, 1.41]	1997
Frank (Anorexigens)	11.1%	56	48	0.65 [0.41, 1.04]	1997
Kawut	2.9%	79	5	0.35 [0.12, 0.99]	2005
Saeed	19.6%	106	234	0.86 [0.64, 1.16]	2011
Ngian	1.7%	36	81	0.20 [0.05, 0.78]	2012
COMPERA registry	30.1%	528	272	0.79 [0.66, 0.94]	2013
Total (95% CI)	**100.0%**	**959**	**771**	**0.69 [0.57, 0.82]**	

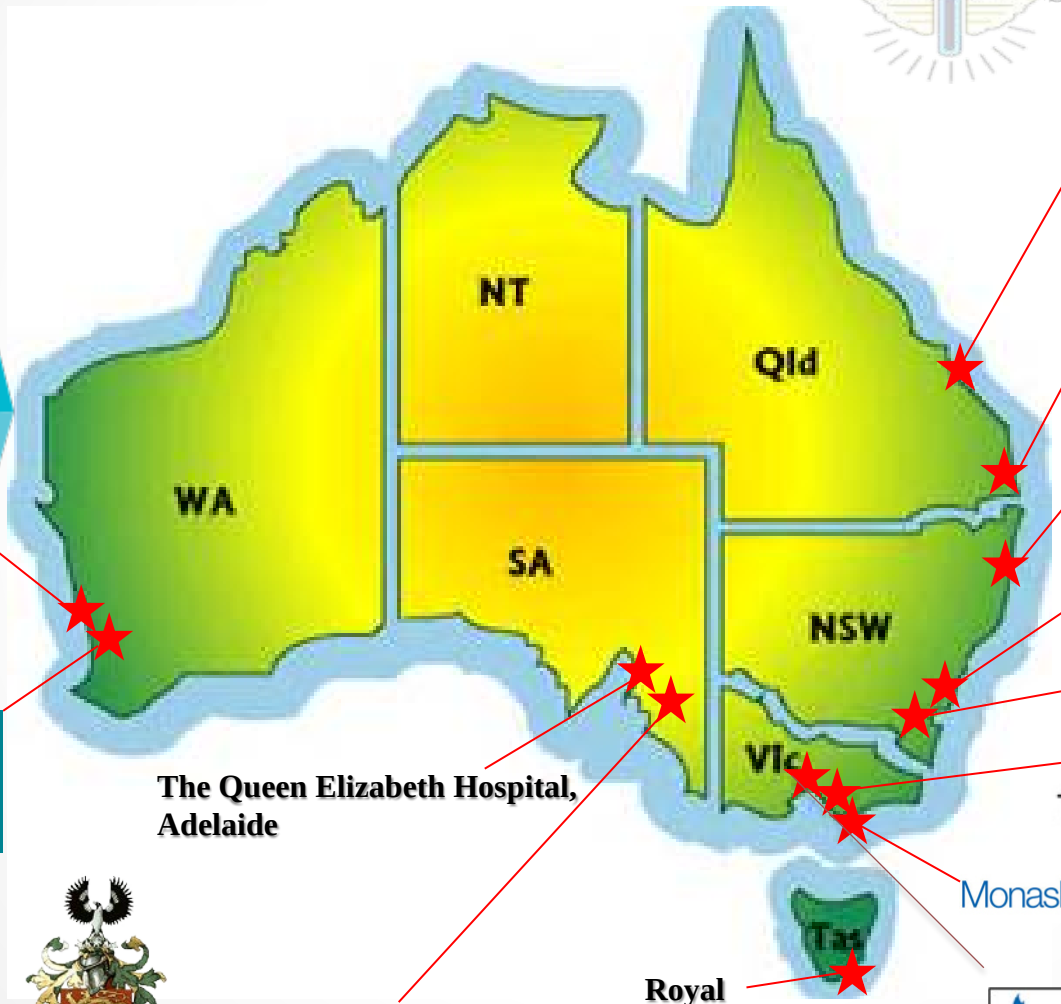
Heterogeneity: $I^2 = 28\%$

Test for overall effect: $Z = 4.02$ ($P < 0.0001$)



No RCTs to date …

SPHInX Study Sites



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Adelaide

FIONA STANLEY hospital

Institute for
Respiratory
Health, Perth

Conclusion

- Systemic sclerosis – early diffuse? ✓
- Pulmonary hypertension. ✓
- Differential diagnosis:
  - Pulmonary arterial hypertension? ✓
  - Hypoxic lung disease (emphysema +ILD – although neither is probably severe enough to cause PH)?
  - Chronic thromboembolic pulmonary hypertension for which surgery would be an option?
  - Contribution of L heart disease?
- Applied for macitentan 10mg/d
- Consider addition of sildenafil
- Likely to need warfarin indefinitely given +LAC
- Likely to have a poor prognosis given emphysema/ILD and PAH
- Candidate for transplantation?

Acknowledgements

Susanna Proudman
Wendy Stevens
Mandana Nikpour
Jo Sahhar
Gene Ngian
Peter Youssef
Peter Nash
Jane Zochling
Janet Roddy
Jenny Walker
Catherine Hill
Vivek Thakkar
Nava Ferdowsi
Gemma Strickland
Kathie Tymms
Allan Sturgess
Les Schrieber
Rodger Laurent

Gabor Major
David Prior
David Celermajer
Eli Gabbay
Nicole Goh
Tamera Corte
Laurie Clemens
Pravin Hissaria
Maureen Rischmueller
Karen Patterson
All referring rheumatologists & physicians
Nursing staff

<u>Nurses & Admin:</u>
Candice Rabusa - Project Officer/data analyst
Michelle Wilson
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