Pulmonary hypertension—
the rheumatologist’s perspective

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and
Australian Scleroderma Interest Group
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
  o Smoker 30 pack years until 2013
  o 3 standard drinks/week

• Past history:
  o Testicular cancer 1987
  o Multiple fractures

• Progressive exertional dyspnoea (FC II)
  o On walking up hills
  o Able to perform ADLs
  o Productive cough in the mornings
  o Using portable oxygen concentrator

• Medications
  o Ranitidine 300mg/d
  o Triotropium 18mcg daily, Seretide, DuroTuss, Salbutamol
Pulmonary function tests

6 minute walk test: 483m, O₂ 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**
- Giant capillaries
- Microhaemorrhages
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
- Interstitial fibrosis
- Cardiac
- Renal
- PAH

**Vasculopathy**
- Gastric Antral Vascular Ectasia

**Interstitial fibrosis**
- Cardiac

**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 skin changes limited to upper limbs, face
- Dilated nailfold capillaries
- Calcinosi, Telangiectasia

- Oesophageal dysmotility
- Clinically significant interstitial lung disease less frequent

- Anti-centromere
- A lower incidence of Scl-70

*previously known as CREST syndrome
Systemic sclerosis subsets – defined by extent of skin involvement

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

*previously known as CREST syndrome*
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
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

Vasoconstriction

In situ thrombosis

Vascular remodelling

Pulmonary Hypertension

Pulmonary hypertension is characterized by high blood pressure in the arteries that transport blood from the heart to the lungs. A heart affected by pulmonary hypertension must work harder than usual to pump blood to the lungs. This can cause enlargement of the right chambers, decreased lung function and backward leakage through the tricuspid valve. The affected arteries experience high blood pressure, although overall blood pressure may be healthy.
Schematic Progression of PAH

- Pre-symptomatic/Compensated
- Symptomatic/ Decompensating
- Declining/ Decompensated

**CO**

**PAP**

**PVR**

**Symptom Threshold**

**Right Heart Dysfunction**

**Time**

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:
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/m²
- pulmonary vascular resistance (PVR) 3.32 Wood Units
- no shunt
- trivial coronary artery disease

*Now known as pulmonary arterial wedge pressure (PAWP)*
<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>PAPm ≥25 mmHg</td>
<td>All</td>
</tr>
<tr>
<td>Pre-capillary PH</td>
<td>PAPm ≥25 mmHg</td>
<td>1. Pulmonary arterial hypertension&lt;br&gt;3. PH due to lung diseases&lt;br&gt;4. Chronic thromboembolic PH&lt;br&gt;5. PH with unclear and/or multifactorial mechanisms</td>
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<tr>
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<td>PAWP ≤15 mmHg</td>
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<tr>
<td>Post-capillary PH</td>
<td>PAPm ≥25 mmHg</td>
<td>2. PH due to left heart disease&lt;br&gt;5. PH with unclear and/or multifactorial mechanisms</td>
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<tr>
<td></td>
<td>PAWP &gt;15 mmHg</td>
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<tr>
<td>Isolated post-capillary PH</td>
<td>DPG &lt;7 mmHg and/or PVR ≤3 WU&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>(Ipc-PH)</td>
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<tr>
<td>Combined post-capillary and pre-capillary PH (Cpc-PH)</td>
<td>DPG ≥7 mmHg and/or PVR &gt;3 WU&lt;sup&gt;c&lt;/sup&gt;</td>
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</tbody>
</table>

NB: “Exercise PH” removed

ESC/ERS Guidelines,<br>Galie et al. European Heart Journal 2015
<table>
<thead>
<tr>
<th>Section</th>
<th>Subsection</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pulmonary arterial hypertension</td>
<td>1.1 Idiopathic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.2 Heritable</td>
<td></td>
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<tr>
<td></td>
<td>1.2.1 BMPR2 mutation</td>
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<td></td>
<td>1.2.2 Other mutations</td>
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<td></td>
<td>1.3 Drugs and toxins induced</td>
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<td></td>
<td>1.4 Associated with:</td>
<td></td>
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<tr>
<td></td>
<td>1.4.1 Connective tissue disease</td>
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<td>1.4.2 Human immunodeficiency virus (HIV) infection</td>
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<td>1.4.3 Portal hypertension</td>
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<td>1.4.4 Congenital heart disease (Table 6)</td>
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<td></td>
<td>1.4.5 Schistosomiasis</td>
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<tr>
<td>1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis</td>
<td>1'.1 Idiopathic</td>
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<tr>
<td></td>
<td>1'.2 Heritable</td>
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<td></td>
<td>1'.2.1 ELF2AK4 mutation</td>
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<td>1'.2.2 Other mutations</td>
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<td>1'.3 Drugs, toxins and radiation induced</td>
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<td></td>
<td>1'.4 Associated with:</td>
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<tr>
<td></td>
<td>1'.4.1 Connective tissue disease</td>
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<td></td>
<td>1'.4.2 HIV infection</td>
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<tr>
<td>1&quot;. Persistent pulmonary hypertension of the newborn</td>
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<tr>
<td>2. Pulmonary hypertension due to left heart disease</td>
<td>2.1 Left ventricular systolic dysfunction</td>
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<td></td>
<td>2.2 Left ventricular diastolic dysfunction</td>
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<td>2.3 Valvular disease</td>
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<td></td>
<td>2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies</td>
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<td></td>
<td>2.5 Congenital /acquired pulmonary veins stenosis</td>
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<tr>
<td>3. Pulmonary hypertension due to lung diseases and/or hypoxia</td>
<td>3.1 Chronic obstructive pulmonary disease</td>
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<td></td>
<td>3.2 Interstitial lung disease</td>
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<td>3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
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<td></td>
<td>3.4 Sleep-disordered breathing</td>
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<td>3.5 Alveolar hypoventilation disorders</td>
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<td>3.6 Chronic exposure to high altitude</td>
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<td>3.7 Developmental lung diseases (Web Table III)</td>
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<tr>
<td>4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions</td>
<td>4.1 Chronic thromboembolic pulmonary hypertension</td>
<td></td>
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<tr>
<td></td>
<td>4.2 Other pulmonary artery obstructions</td>
<td></td>
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<tr>
<td></td>
<td>4.2.1 Angiosarcoma</td>
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<td>4.2.2 Other intravascular tumors</td>
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<td></td>
<td>4.2.3 Arteritis</td>
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<td></td>
<td>4.2.4 Congenital pulmonary arteries stenoses</td>
<td></td>
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<td></td>
<td>4.2.5 Parasites (hydatidosis)</td>
<td></td>
</tr>
<tr>
<td>5. Pulmonary hypertension with unclear and/or multifactorial mechanisms</td>
<td>5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy</td>
<td></td>
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<tr>
<td></td>
<td>5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis</td>
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<tr>
<td></td>
<td>5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders</td>
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<tr>
<td></td>
<td>5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension</td>
<td></td>
</tr>
</tbody>
</table>
PH Class 1

PH Class 3

PH Class 4

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 dysfunciton due to myocardial involvement
Clinically evident in 15-35%
Subclinical in up to 75%

Antiphospholipid antibodies

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

Pulmonary veno-occlusive disease (PVOD)

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

#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

3818 patients
- RHC-defined PAH
- 58 ±14 years
- 82 % women
- SSc duration 9±8 years

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

Avouac et al., 2009
## Characteristics of patients in the ASCS\(^1\) (n=1,186)

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

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)

54 (55.7%) SSc-related
43 (44.3%) non-SSc related*

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 ratio
- Oxygen desaturation with exercise
- Increased baseline NT-pro-BNP**#
- Pericardial effusion
- RBB
- Raised ESR, IgG

**No increased risk**
- Rodnan total skin score
- Frequency of GI involvement
- Frequency of pulmonary fibrosis
- Mean FVC
- Anti-centromere Ab?

*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

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

The UK CTD-PAH registry

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

‘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 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

<table>
<thead>
<tr>
<th>Peak tricuspid regurgitation velocity (m/s)</th>
<th>Presence of other echo ‘PH signs’</th>
<th>Echocardiographic probability of pulmonary hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.8 or not measurable</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>≤2.8 or not measurable</td>
<td>Yes</td>
<td>Intermediate</td>
</tr>
<tr>
<td>2.9–3.4</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>&gt;3.4</td>
<td>Not required</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A: The ventricles</th>
<th>B: Pulmonary artery</th>
<th>C: Inferior vena cava and right atrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle/left ventricle basal diameter ratio &gt;1.0</td>
<td>Right ventricular outflow Doppler acceleration time &lt;105 msec and/or midsystolic notching</td>
<td>Inferior cava diameter &gt;21 mm with decreased inspiratory collapse (&lt;50 % with a sniff or &lt;20 % with quiet inspiration)</td>
</tr>
<tr>
<td>Flattening of the interventricular septum (left ventricular eccentricity index &gt;1.1 in systole and/or diastole)</td>
<td>Early diastolic pulmonary regurgitation velocity &gt;2.2 m/sec</td>
<td>Right atrial area (end-systole) &gt;18 cm²</td>
</tr>
</tbody>
</table>

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

NT-proBNP correlates with haemodynamics at RHC

A. Correlation of NT-proBNP with mPAP

B. Correlation of NT-proBNP with mRAP

C. Correlation of NT-proBNP with PVR

Proposed Screening Algorithm (ASIG Proposed)

SSc Patients

NT-proBNP & PFTs

Screen positive
NT-proBNP ≥210 pg/ml
and/or DLCO <70% + FVC/DLCO ≥1.8

Screen negative
NT-proBNP <210 pg/ml
and DLCO ≥70% + FVC/DLCO <1.8

ECHO, 6MWD, HRCT lung, etc.

Right Heart Catheterisation

PAH

No PAH

Low probability of PAH

Repeat in 12 months

PPV: 22%
NPV: 98%

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

**DETECT decision tree**

**Step 1**
Non-echo variables:
- FVC/DLCO
- Telangiectasias
- serum ACA
- serum NT-proBNP
- serum urate
- right axis deviation

Total risk points > 300?
- Yes: No referral to echocardiography
- No: No referral to RHC

**Step 2**
Total risk points from step 1 plus echo variables:
- right atrium area
- TR velocity

Total risk points > 35?
- Yes: Referral to RHC
- No: No referral to RHC

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

**Positive**

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

*Coughlan 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).

Individual risk points in Step 1

- FVC % predicted / DLCO % predicted
- Current / past telangiectasias
- Serum ACA
- Serum NTproBNP
- Serum urate
- ECG: right axis deviation

Total risk points from Step 1

Individual risk points in Step 2

- Right atrium area
- TR velocity

Total risk points from Step 2

No referral → Referral to echocardiography

No referral → Referral to right heart catheterisation


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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.
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
  - 27 (37%) WHO group1 PH (PAH)
  - 39 (53%) PH
    - 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

<table>
<thead>
<tr>
<th></th>
<th>DETECT n=61</th>
<th>ESC/ERS n=58</th>
<th>ASIGN\text{NEW} n=61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>100% (87.2-100)</td>
<td>96.3% (81-99.9)</td>
<td>100% (87.2-100)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>35.3% (19.7-53.5)</td>
<td>29.0% (19.7-53.3)</td>
<td>47.1% (29.8-64.9)</td>
</tr>
<tr>
<td>PPV (95% CI)</td>
<td>55.1% (40.2-69.3)</td>
<td>54.2% (39.2-68.6)</td>
<td>60% (44.3-74.3)</td>
</tr>
<tr>
<td>NPV (95% CI)</td>
<td>100% (63.1-100)</td>
<td>90.0% (55.5-99.7)</td>
<td>100% (79.4-100)</td>
</tr>
<tr>
<td>Referral rate for RHC</td>
<td>80%</td>
<td>81%</td>
<td>68%</td>
</tr>
</tbody>
</table>
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.

- $\text{ASIG}_{\text{NEW}}$ 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 $\text{ASIG}_{\text{NEW}}$ 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\textsubscript{NEW})**

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

NNS = number needed to screen. All costs are in Australian Dollars.
Proposed Screening Algorithm (ASIG\textsubscript{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

- selexipag
- macitentan
- riociguat

Figure 1. Pathophysiology and therapeutics in SSc-PAH
Vessel drawing taken from Gaine S. JAMA 2000; labels and text by Dr Nikpour
ESC/ERS Guidelines,
Galie et al. European Heart Journal 2015

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.

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

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

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

*Consider also balloon atrial septostomy.
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

<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>Class&lt;sub&gt;a-level&lt;sup&gt;b&lt;/sub&gt;</th>
<th>Ref.©</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WHO-FC II</td>
<td>WHO-FC III</td>
</tr>
<tr>
<td>Ambrisentan + tadalafil&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Other ERA + PDE-5i</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Bosentan + sildenafil + i.v. epoprostenol</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bosentan + i.v. epoprostenol</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + s.c. treprostinil</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + other i.v. prostacyclin analogues</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

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
  o 6 RCTs with heterogeneous results
  o Benefit in meta-analysis

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


  o In Australia, patient funded or obtained on compassionate grounds.
## Stratifying Prognosis in PH

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

ESC/ERS Guidelines, Galie et al. European Heart Journal 2015
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that PAH patients avoid pregnancy</td>
<td>I</td>
<td>C</td>
<td>160, 161</td>
</tr>
<tr>
<td>Immunization of PAH patients against influenza and pneumococcal infection is recommended</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Psychosocial support is recommended in PAH patients</td>
<td>I</td>
<td>C</td>
<td>168</td>
</tr>
<tr>
<td>Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy</td>
<td>IIa</td>
<td>B</td>
<td>153–157</td>
</tr>
<tr>
<td>In-flight O₂ administration should be considered for patients in WHO-FC III and IV and those with arterial blood O₂ pressure consistently &lt; 8 kPa (60 mmHg)</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Excessive physical activity that leads to distressing symptoms is not recommended in PAH patients</td>
<td>III</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

ESC/ERS Guidelines, Galie et al. European Heart Journal 2015
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention</td>
<td>I</td>
<td>C</td>
<td>178</td>
</tr>
<tr>
<td>Continuous long-term O₂ therapy is recommended in PAH patients when arterial blood O₂ pressure is consistently &lt;8 kPa (60 mmHg)</td>
<td>I</td>
<td>C</td>
<td>179</td>
</tr>
<tr>
<td>Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of anorexigenes</td>
<td>IIb</td>
<td>C</td>
<td>84,171, 175–177</td>
</tr>
<tr>
<td>Correction of anaemia and/or iron status may be considered in PAH patients</td>
<td>IIb</td>
<td>C</td>
<td>184</td>
</tr>
<tr>
<td>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)</td>
<td>III</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

ESC/ERS Guidelines, Galie et al. European Heart Journal 2015
# Real-life studies of SSc-PAH – 3 year survival is still poor

<table>
<thead>
<tr>
<th></th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCS* (CTD-PAH)</td>
<td>94%</td>
<td>89%</td>
<td>73%</td>
</tr>
<tr>
<td>Williams et al. (SSc-PAH)</td>
<td>81%</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Condliffe et al. (SSc-PAH)</td>
<td>78%</td>
<td>58%</td>
<td>47%</td>
</tr>
<tr>
<td>Chung et al. (CTD-PAH)</td>
<td>86%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Royal Perth Hospital, RAH, FMC, TQE, St Vincent’s Hospital Melbourne and Monash Medical Centre

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

### Mortality – multivariable analysis

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

*Most common combination was bosentan and sildenafil*
## Warfarin associated with improved survival independently of baseline PAH severity

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

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

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

No RCTs to date …
SPHInX Study Sites

- Coffs Harbour
- Royal Prince Alfred Hospital, Sydney
- Royal Hobart Hospital
- Monash Medical Centre, Clayton
- Liverpool Hospital, Sydney
- The Alfred Hospital, Melbourne
- The Queen Elizabeth Hospital, Adelaide
- Royal Adelaide Hospital
- Gold Coast Cardiology, Gold Coast University Hospital
- Institute for Respiratory Health, Perth
- Sunshine Coast Rheumatology Research Unit
- St Vincent’s Hospital, Melbourne
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

Nurses & Admin:
Candice Rabusa - Project Officer/data analyst
Michelle Wilson
Molla Huq
Kate Scott

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

An initiative of:

Australian Scleroderma Interest Group

Scleroderma Australia

Arthritis Australia