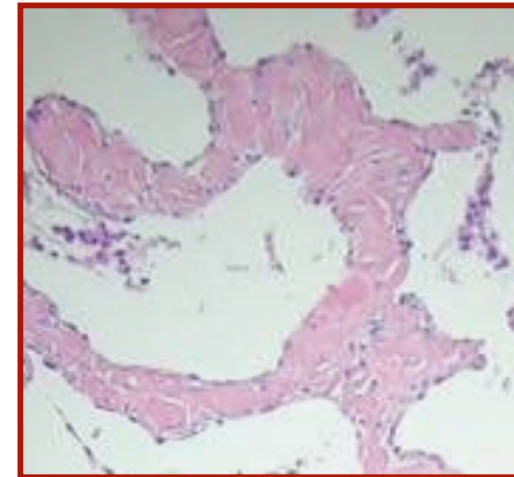
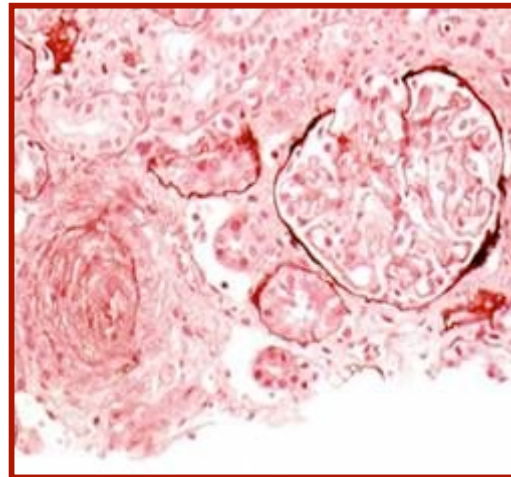


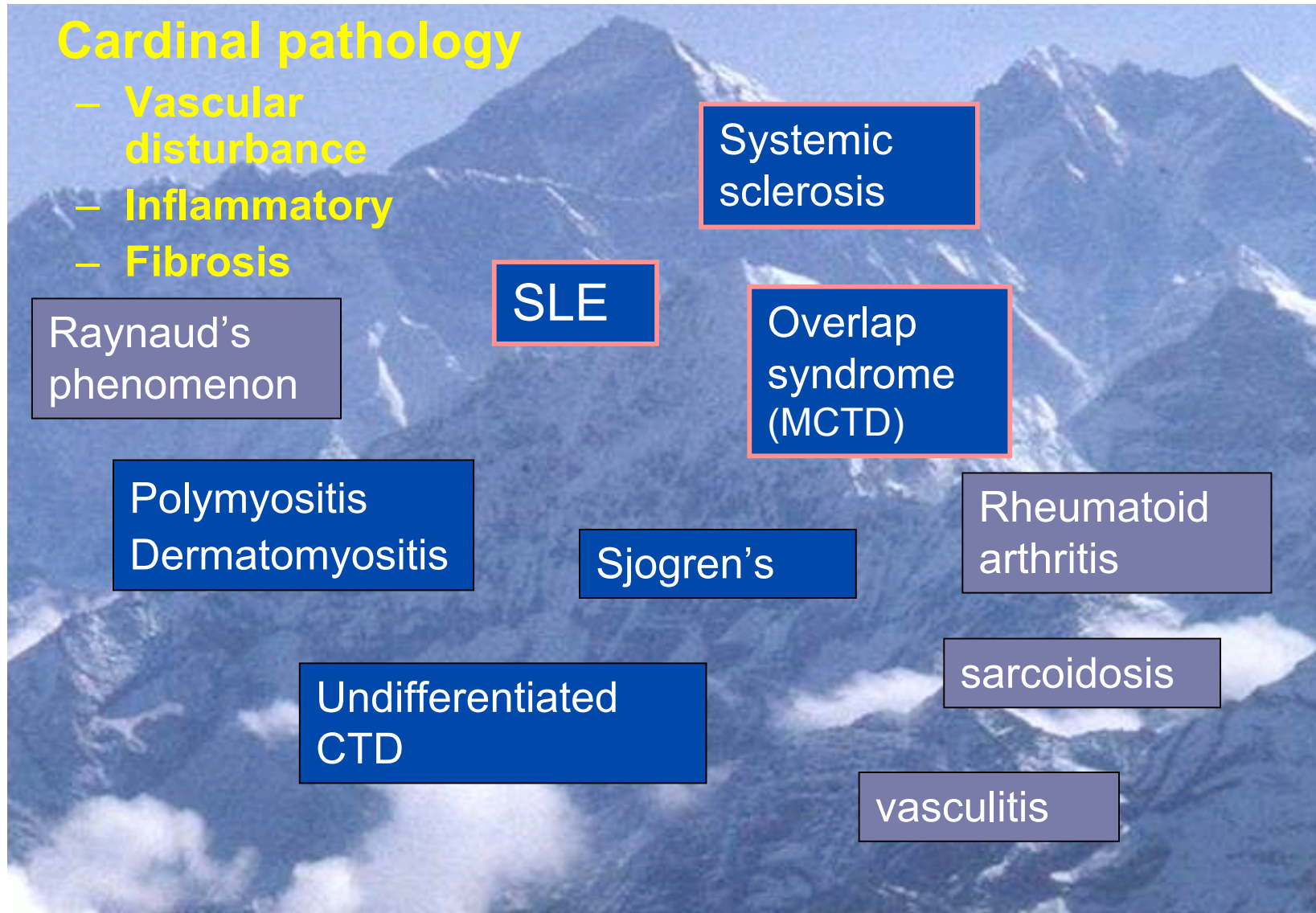
Connective tissue disease associated pulmonary hypertension



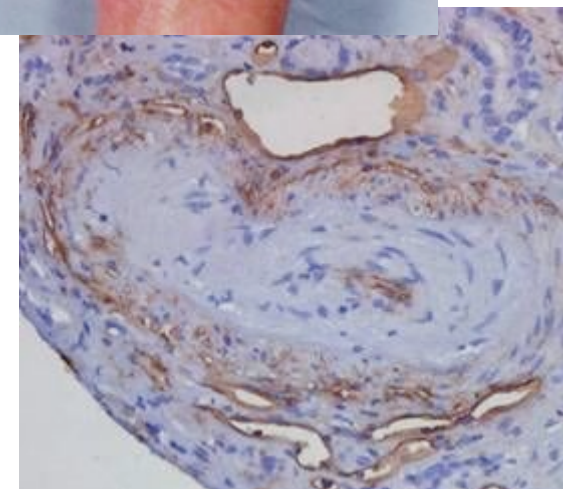
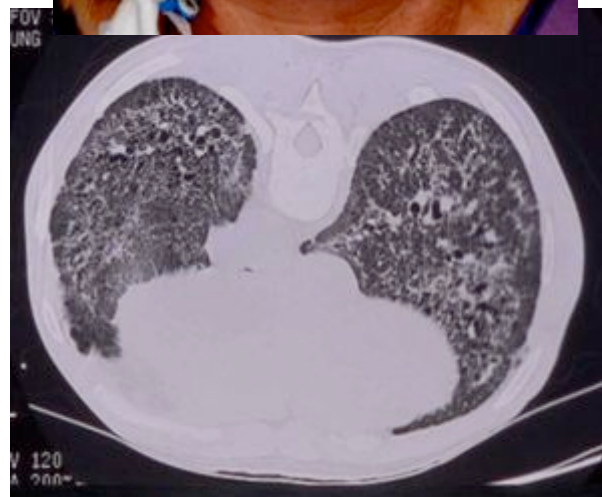
Christopher P. Denton PhD FRCP
Professor of Experimental Rheumatology
University College London



Spectrum of connective tissue disease



Diffuse cutaneous systemic sclerosis



Limited cutaneous systemic sclerosis

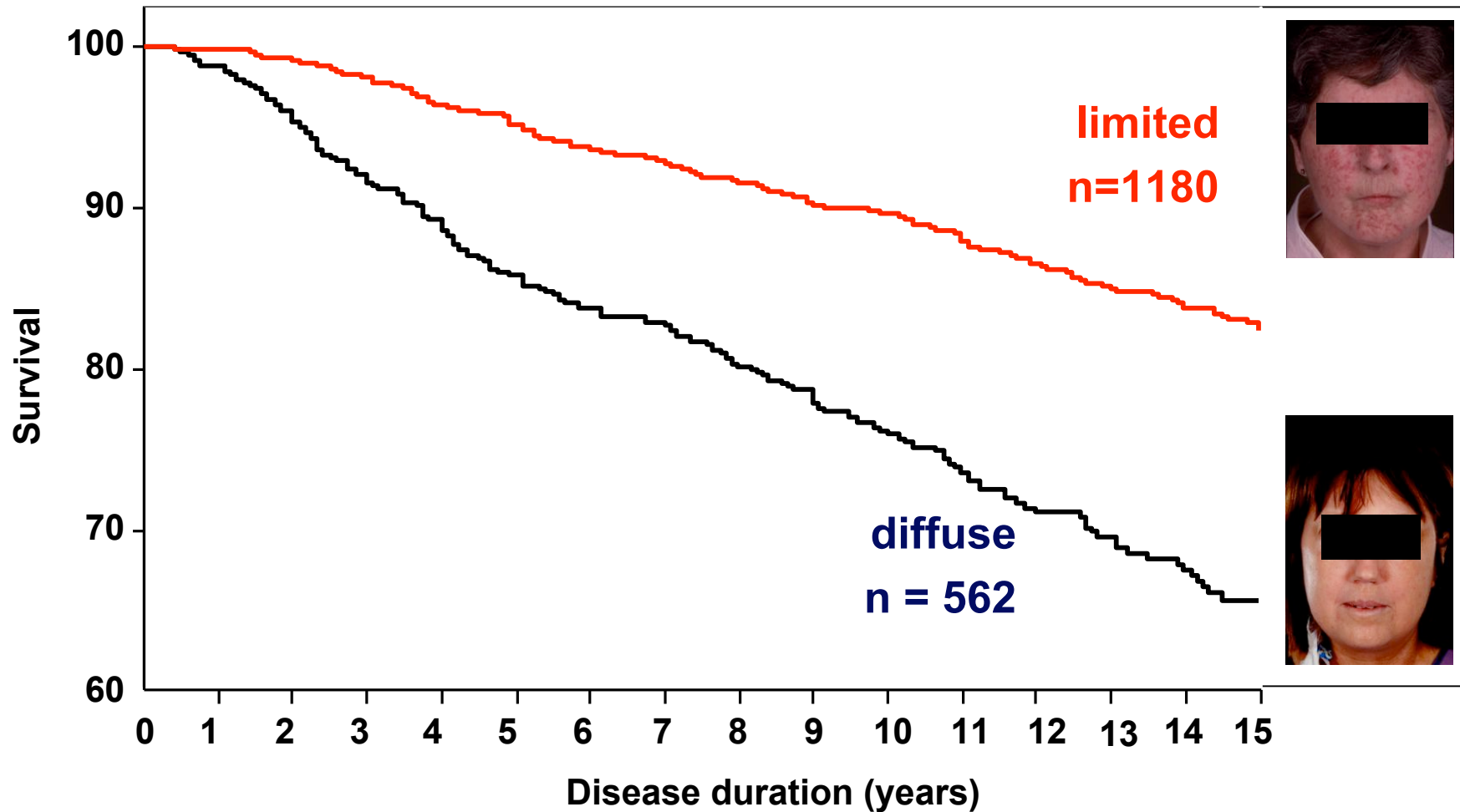


Royal Free Scleroderma Cohort 2006

	Male	Female	Total
Diffuse*	119 (21%)	443 (79%)	562 (33%)
Limited	182 (15%)	998 (85%)	1180
Total	301 (17%)	1441 (83%)	1742

*225 cases present within 12 months of disease onset
Standardised data collection 6 monthly for first 3 years (dcSSc) then
annually (all cases).

Comparative survival of limited and diffuse cutaneous SSc subsets

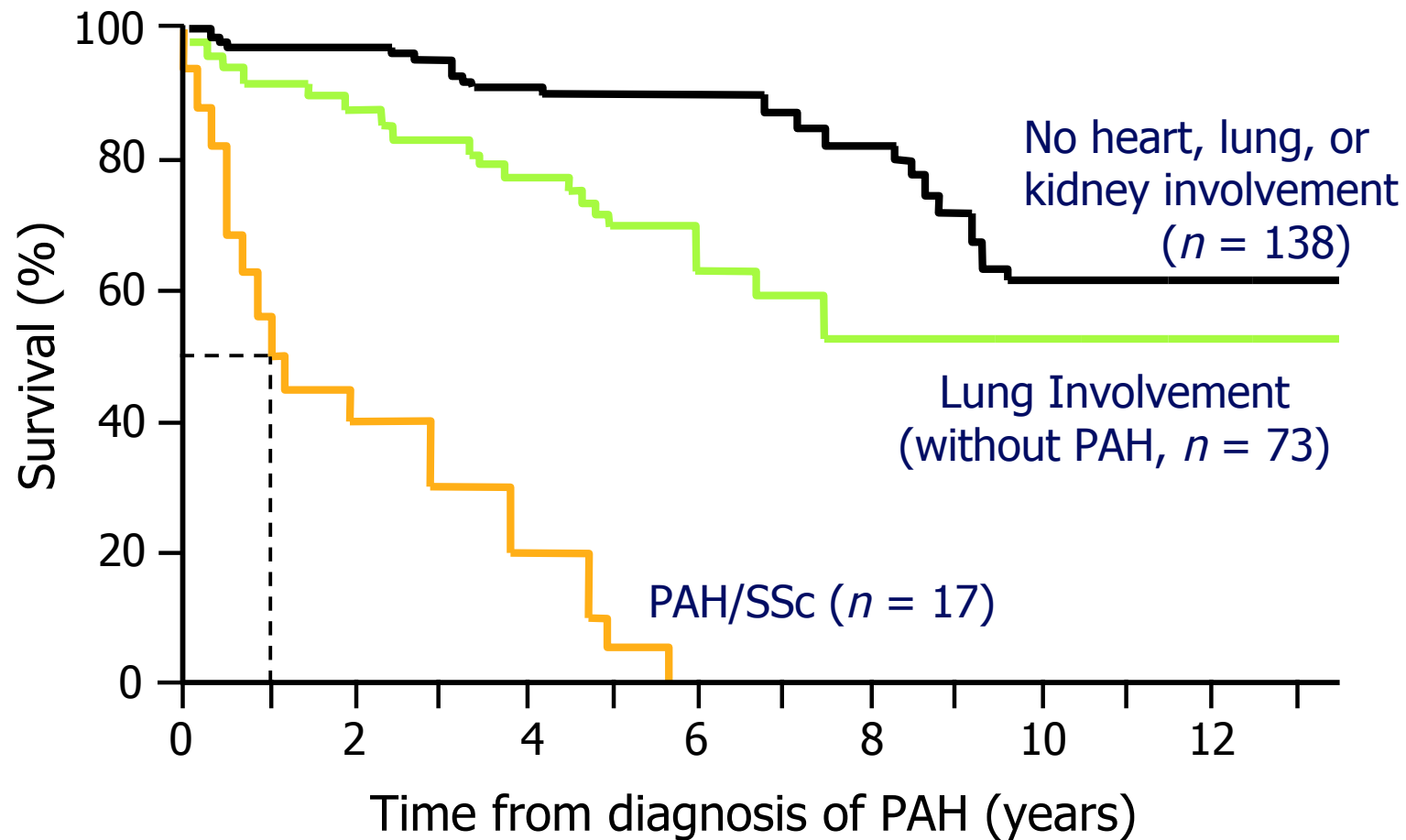


RFH Cohort Data 2007

Causes of Death in SSc (RFH database)

- ◆ 1594 cases SSc ascertained
 - 518 deaths (1990-2002)
 - 302 attributable to SSc
 - 128 pulmonary 42%
 - 52 cardiac 17%
 - 25 gut 8%
 - 23 renal 3%
 - 24 cancer 8%
 - 16 unspecified SSc related 5%
 - 11 septicaemia
 - 6 suicide
 - 3 pancreatitis 7%
 - 1 epistaxis
 - 1 amyloidosis

PAH dramatically affects outcome in SSc



Royal Free Hospital Pulmonary Hypertension Service



Centre for Rheumatology

Maresa Carulli
Lynne Shand
Henry Penn
Svetlana Nihtyanova
Carmen Fonseca

David Abraham
Chris Denton
Carol Black

Department of Cardiology

Gerry Coghlan
Clive Handler
Peter Kabunga
Mark Williams
Raza Akram
David Bloore

Royal Free Hampstead

NHS Trust

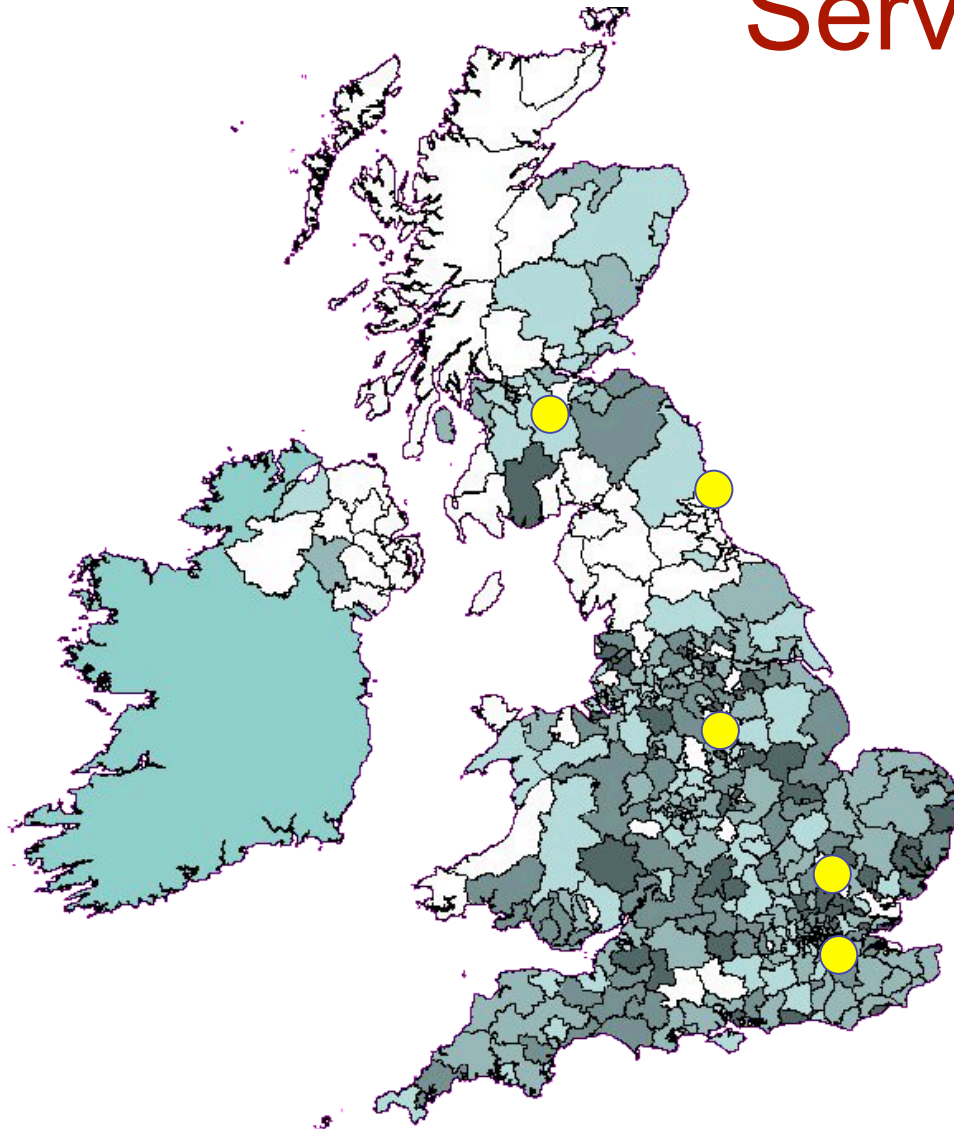


Prevalence of pulmonary arterial hypertension in connective tissue disease

Disease	ECHO prevalence	Catheter/Clinical prevalence
Systemic Sclerosis	20 – 50% ^{1,2}	7.85 – 12% ^{3,4}
Lupus	4 – 43% ^{5,6}	0.9% ³
Rheumatoid Arthritis	20% ⁷	<0.01% ⁸

1. Rheumatismo. 2005; 57: 114
2. Chest 1996;110:1515
3. *Eur J Respir Dis* Vol 59, No 6, 2004
4. *Ann Rheum Dis* 2003; 62: 1088
5. *Lupus*. 2000;9(5):338
6. *Am Heart J* 1995; 129: 510
7. *Rheumatology* 2000;3:1320
8. Post Marketing Surveillance Study (Data on file)

UK National Pulmonary Hypertension Service

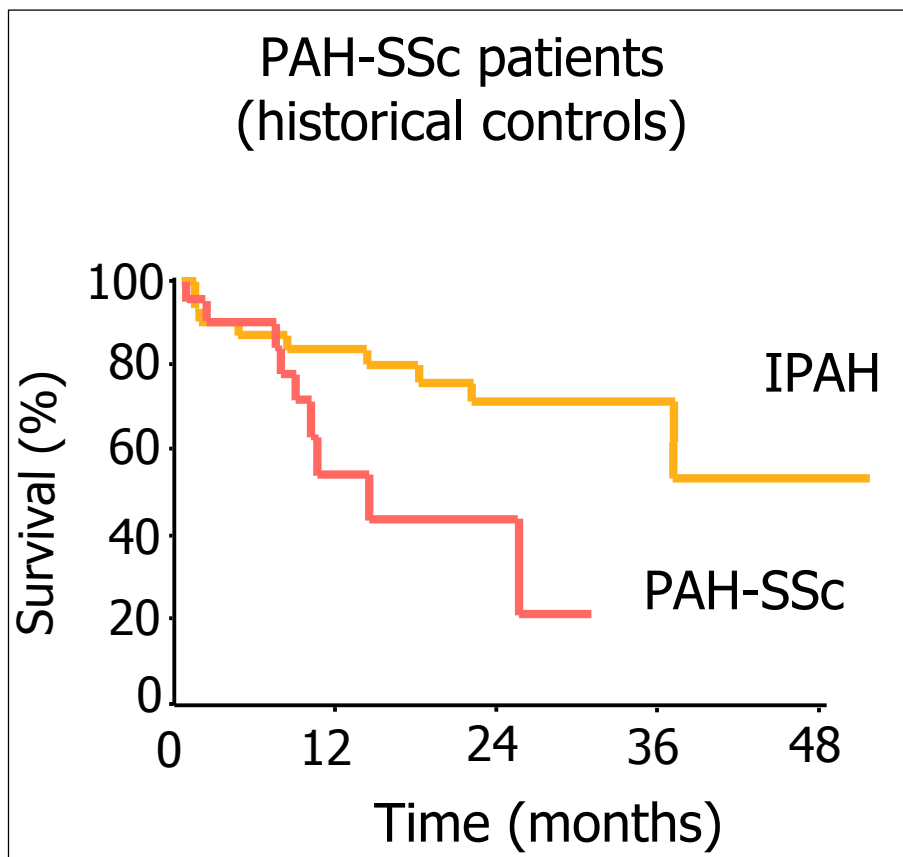


- Glasgow
- Newcastle
- Sheffield
- Cambridge
- London
 - Royal Free
 - Great Ormond Street
 - Hammersmith
 - Brompton

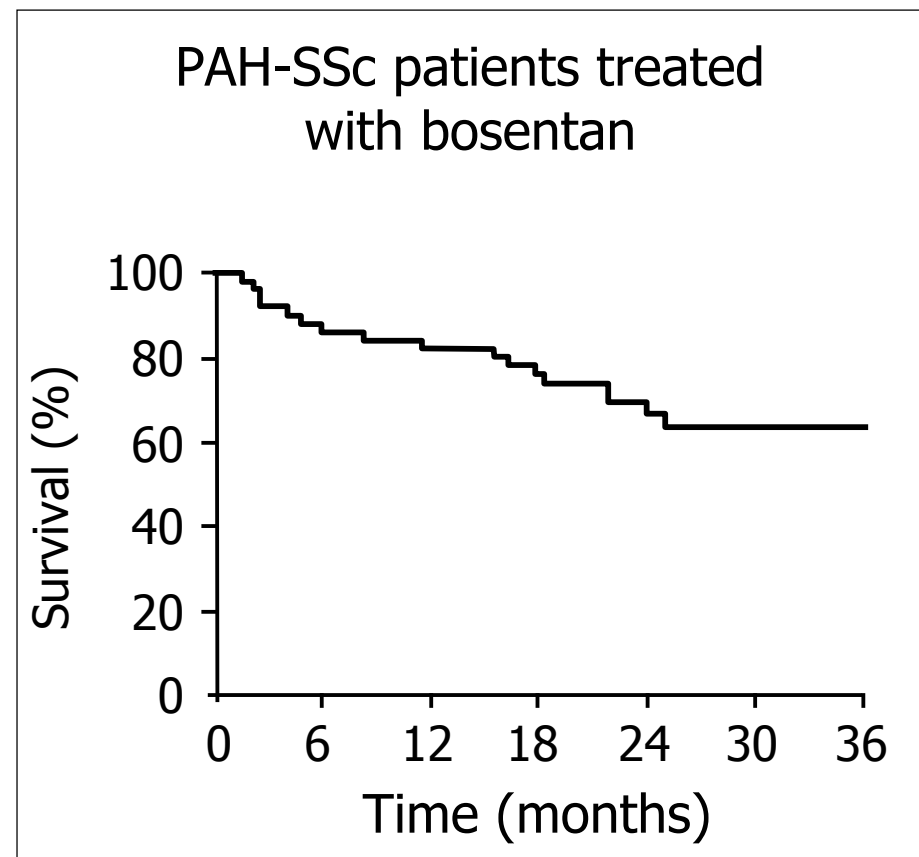
National Survey of CTD PAH

- ◆ Prospective registry of CTD PAH Jan01 – Jun 06
- ◆ 429 CTD-PAH; 59 exercise PH; 24 PVR<240
- ◆ Cohort
 - 315 SSc-PAH (259 isolated)
 - 36 MCTD (28 isolated)
 - 35 SLE (29 isolated)
 - 18 DM/PM (7 isolated)
 - 13 RA (12 isolated)

Survival of PAH-SSc patients treated with bosentan in clinical trials compared with historical controls

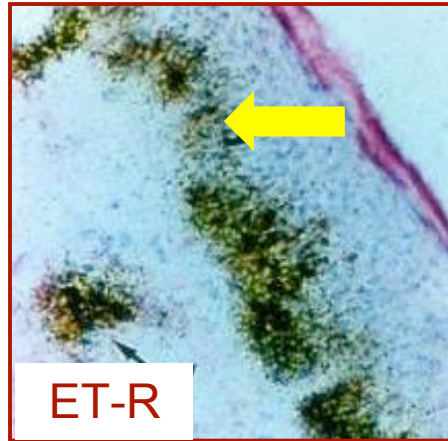


Kawut SM, *et al.* *Chest* 2003; 123:344.

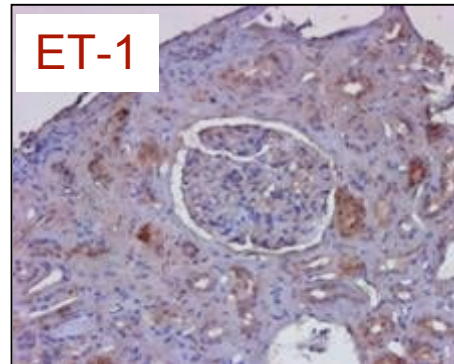


Denton C, *et al.* *Ann Rheum Dis* 65: 1336-1340

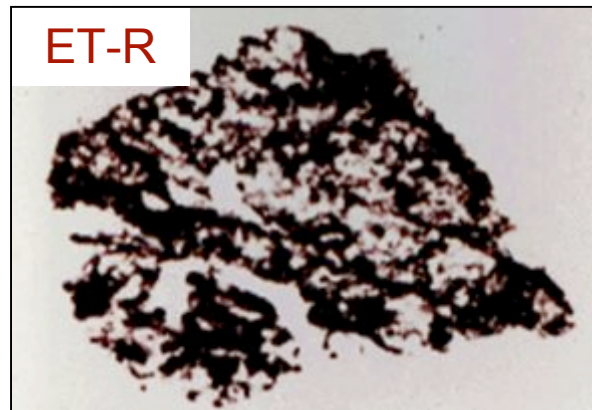
Endothelin axis is upregulated in lesional tissue in systemic sclerosis



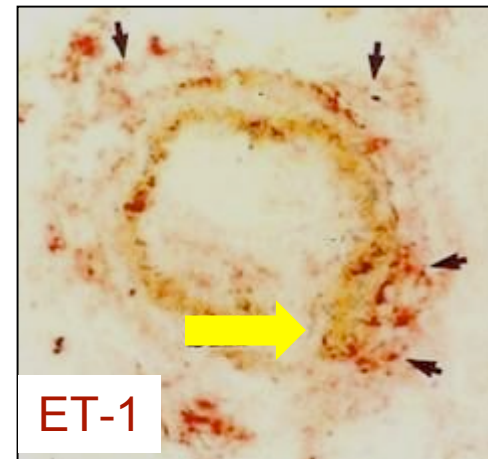
Skin



Kidney



Lung



Pulmonary artery

Vancheeswaran *et al.* **J Rheum** 1995.

Abraham *et al.* **Am J Pathol** 1997;151:831-41.

Denton and Black. **Rheum Dis Clin N America** 2003: 335-49

Denton and Penn (2007, unpublished)

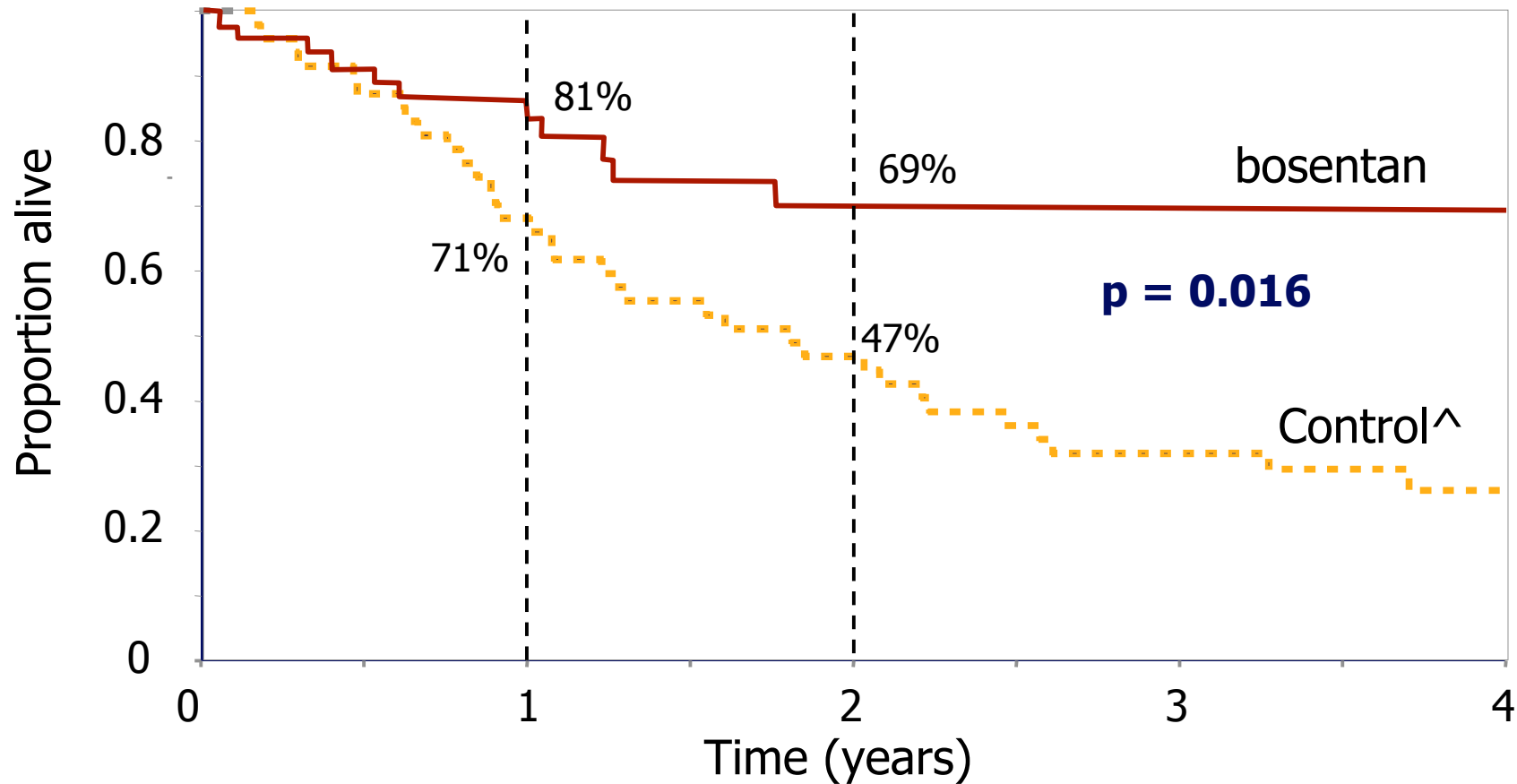
Registry data of bosentan therapy in SSc-PAH: single UK centre

Parameter	Bosentan (<i>n</i> = 45)	Control* (<i>n</i> = 47)
Age (\pm SD)	60 \pm 11	58 \pm 11
Gender (M/F)	7/38	7/40
Diffuse/Limited SSc	2/43	13/34
mRAP \pm SD (mmHg)	8 \pm 6	7 \pm 4
mPAP \pm SD (mmHg)	40 \pm 12	40 \pm 11
CI \pm SD (l/min/m ²)	2.6 \pm 0.7	2.7 \pm 0.9
PVR (dyns/sec/cm ⁵)	613 \pm 345	597 \pm 359
WHO III/IV (%)	29(64%)/16(36%)	37 (79%)/10(21%)

*conventional therapy n=20;
conventional plus iv prostanoid n=27

Williams et al, **Heart**. 2006, 92:926-32

Impact of first-line bosentan therapy on survival in patients with PAH-SSc



^Conventional therapy +/- prostanoids

Williams et al, **Heart**. 2006, 92:926-32

TRUST

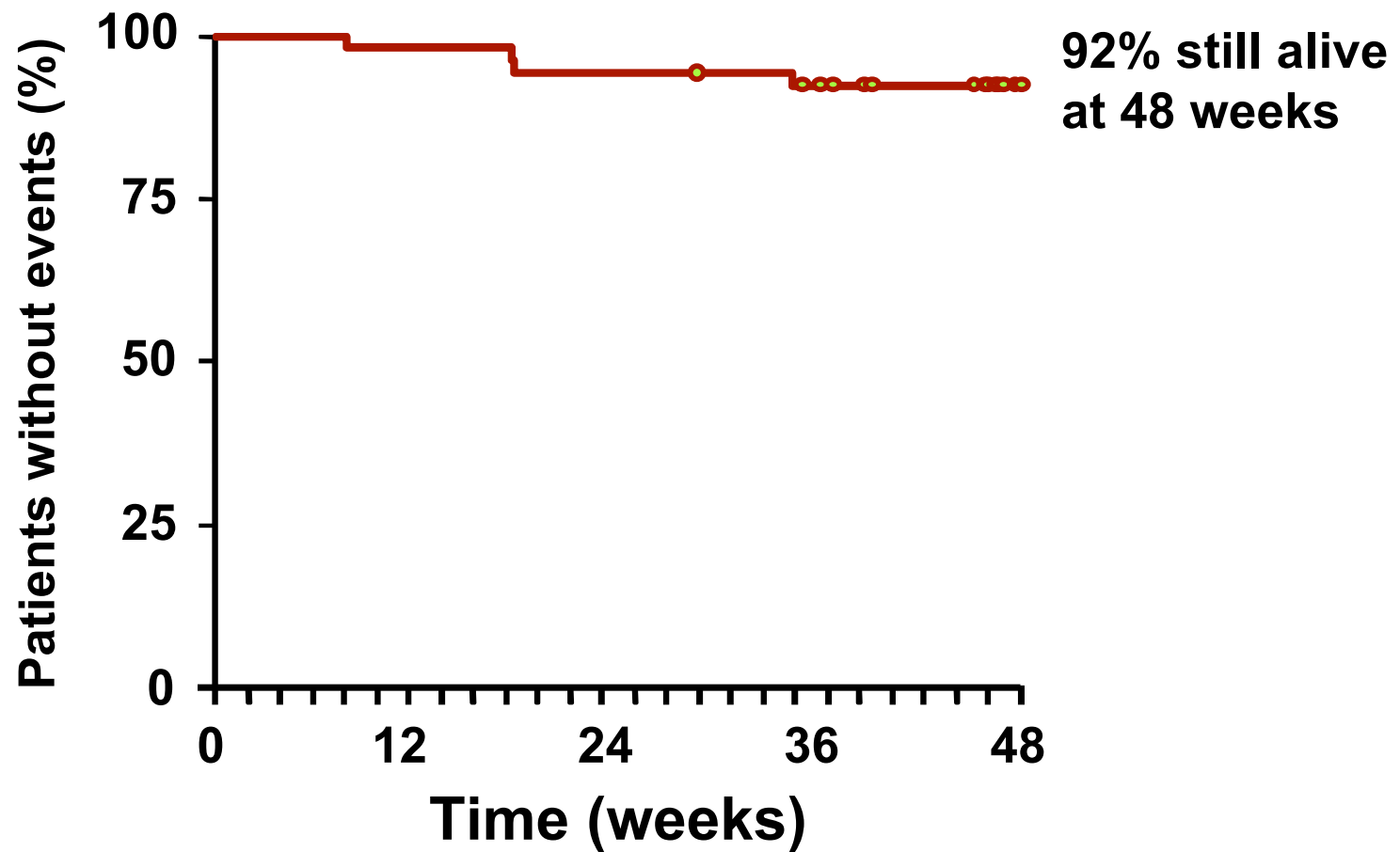
TRacleer Use in PAH associated with Scleroderma and other connective Tissue diseases

- ◆ Evaluate effects of bosentan treatment in PAH-CTD class III patients on:
 - Quality of life (QoL) as measured by SF-36
 - Long-term outcome and time to clinical worsening
 - Safety and tolerability
- ◆ 53 patients
 - SSc, n=42
 - lcSSc=29; dcSSc=13
 - MCTD, n=5
 - SLE, n=6

Denton *et al.* (2007 submitted)

TRUST

Kaplan-Meier survival estimates of patients treated with bosentan



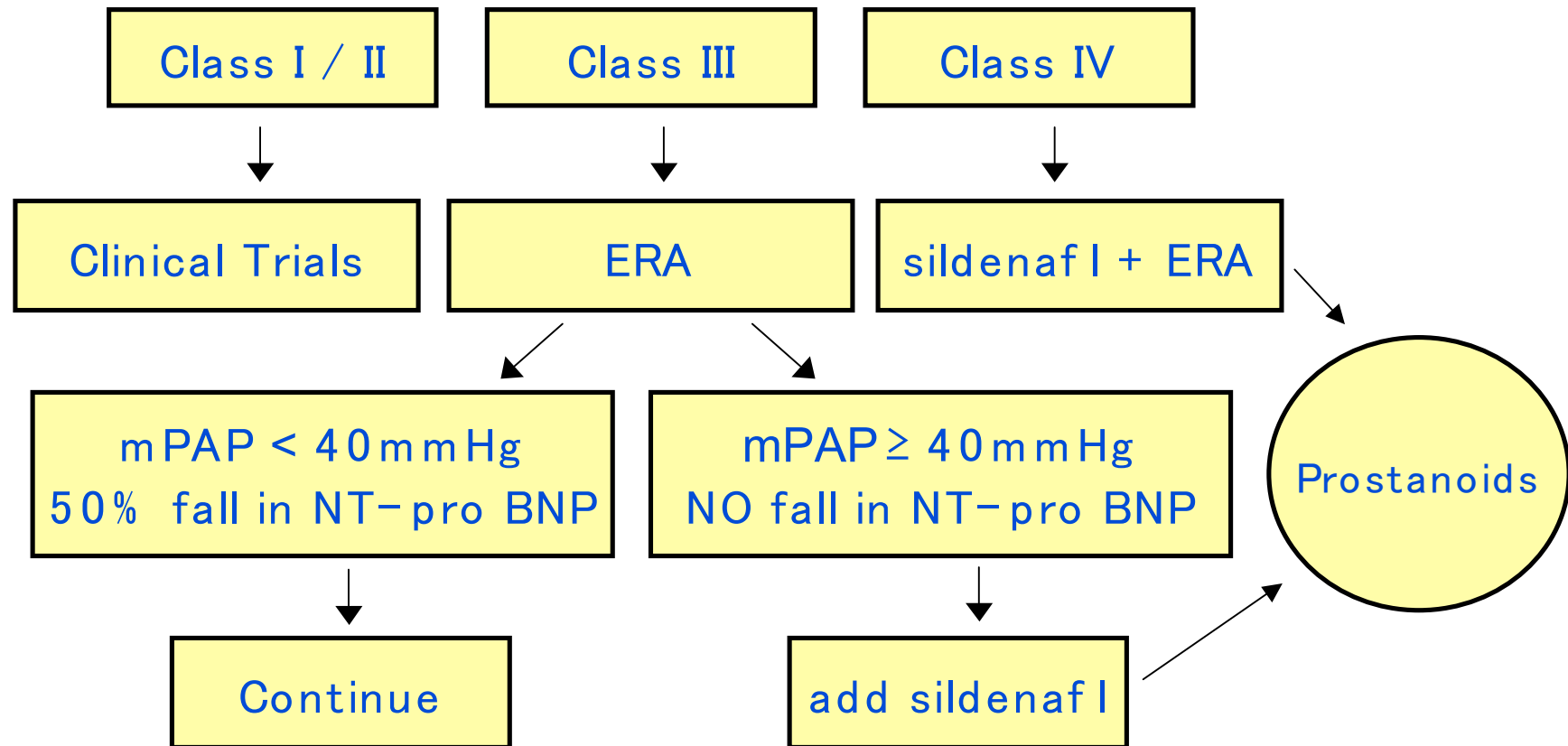
Denton *et al.* (2007 submitted)

Sitaxentan* treatment of PAH-CTD

- ◆ Post-hoc sub-group analysis of pooled data from STRIDE-1, -2 and -4 including 110 cases of PAH-CTD (SSc, SLE, MCTD)
- ◆ Significant increase in 6-MWD vs placebo at 18 weeks ($p = 0.04$) for the 100 mg group.
- ◆ Favourable survival data from clinical trial cohorts – including open label comparison with bosentan in PAH-CTD
- ◆ Registry data awaited – now licensed therapy in EU for advanced PAH

*ET_A subtype-specific endothelin receptor antagonist

SSc-PAH Treatment Algorithm 2007

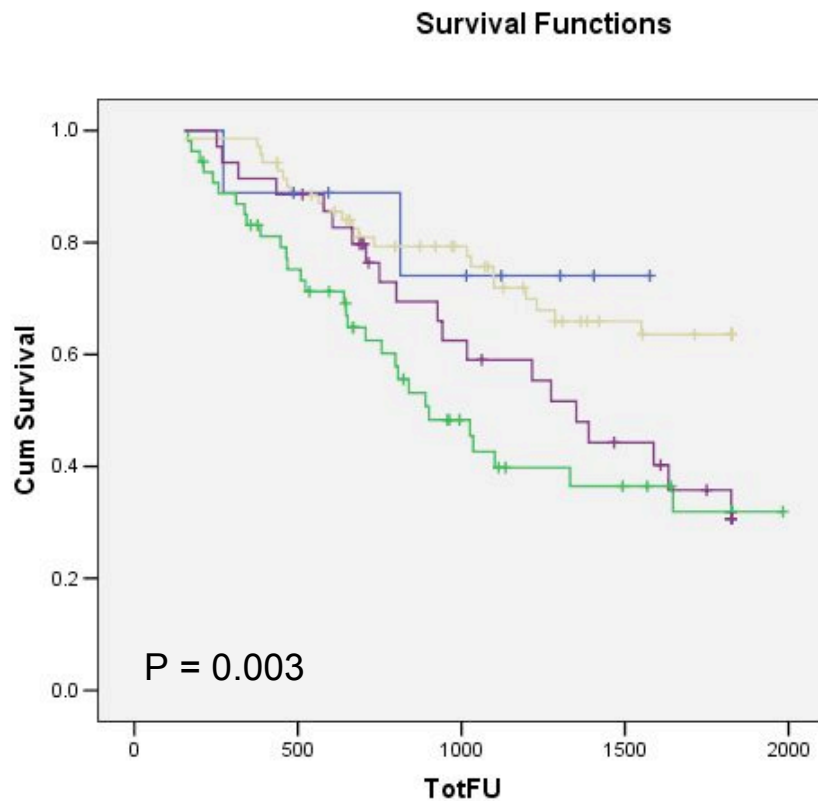


Any secondary deterioration leads to added therapy

Haemodynamic predictors of poor outcome – the gold standard in assessment?

- ◆ 168 PAH-SSc patients who underwent at least two catheters
- ◆ 117 patients with isolated PAH only
- ◆ 49 patients with isolated PAH and a MPAP>40mm Hg
- ◆ Does haemodynamic progression predict survival?

Haemodynamic predictors of outcome in PAH-SSc: mPAP (mmHg)

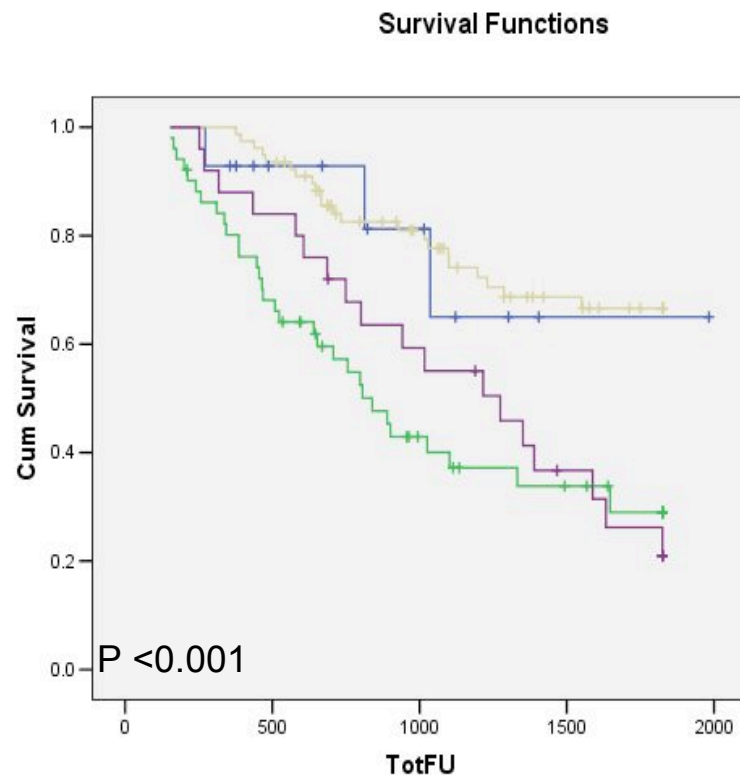


Haemodynamic response	Yr 1	Yr 3	Yr 5
Improve to <40 n=9	90%	74%	74%
Stable <40 n=70	99%	77%	64%
Stable >40 n=54	83%	43%	32%
Worsen to >40 n=35	91%	59%	31%

N=168, RFH cohort 2006

RFH Cohort Data 2007

Survival and change in PVR (dynes/s/cm⁵) with time



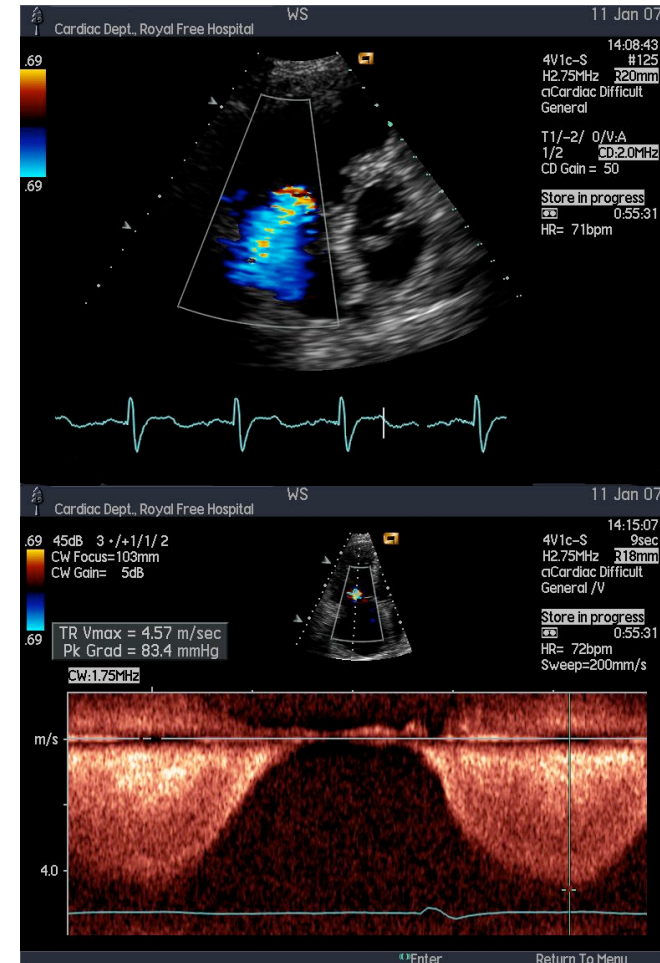
Haemodynamic response	Yr 1	Yr 3	Yr 5
PVR improved to < 645 n=14	93%	65%	65%
PVR stable <645 n= 78	100%	80%	67%
PVR stable >645 n=51	80%	40%	29%
PVR worsened to >645 n=25	88%	55%	21%

N=168, RFH cohort 2006
Median PVR = 645 dynes/s/cm⁵

RFH Cohort Data 2007

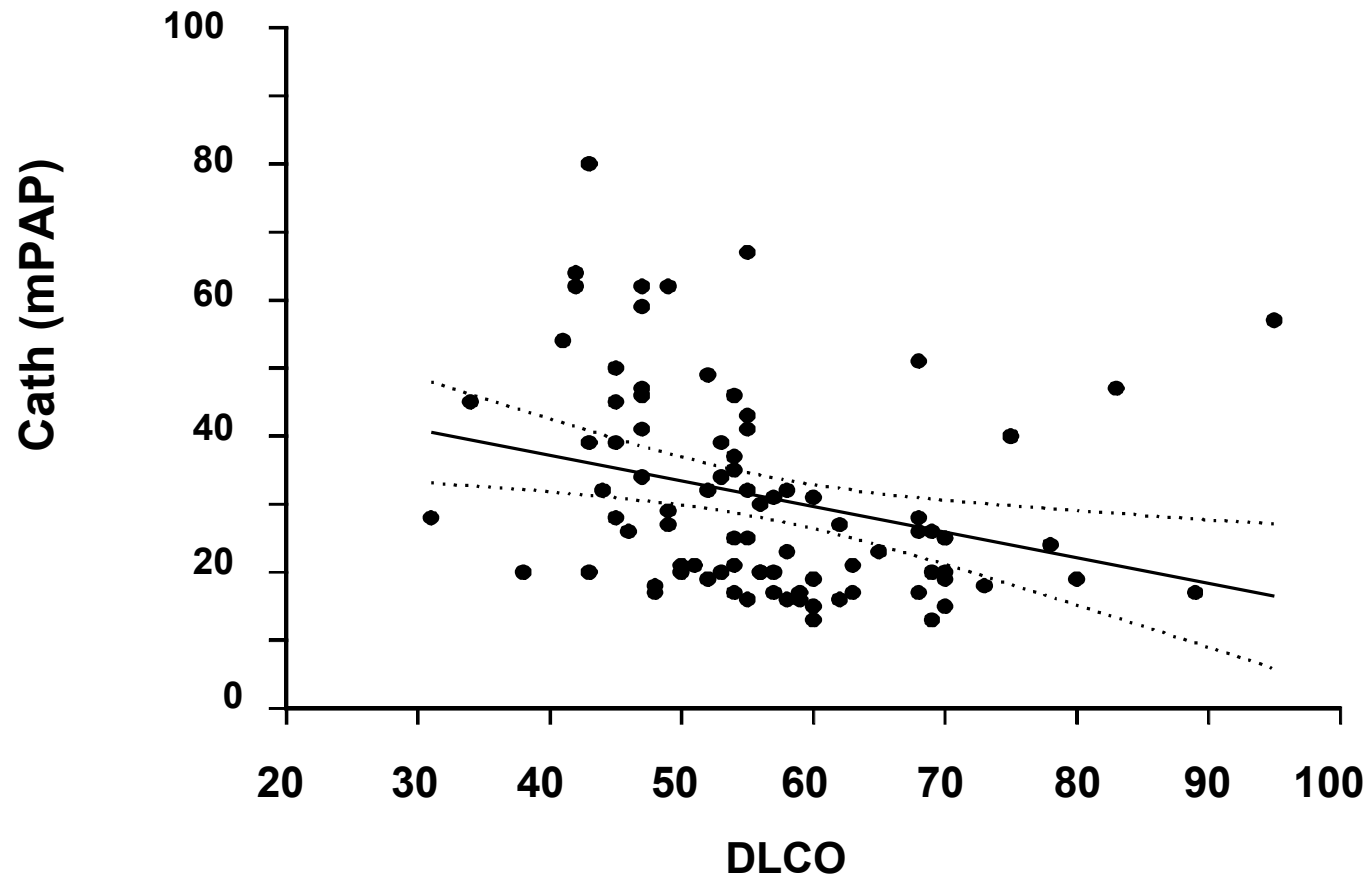
Screening for PAH in SSc

- ◆ 3 to 16% of SSc patients have PAH^{1,2}
- ◆ Untreated mortality is 30% pa or above³
- ◆ Disease modifying therapies are available
- ◆ Annual echo recommended by ECS⁴



1. *Nippon Rinsho* Vol 59, No 6, 2001; 2. *Ann Rheum Dis* 2003; 62: 1088
3. *Br J Rheumatol.* 1996; **35**: 989; 4. *Eur Heart J* 2004; 25: 2243

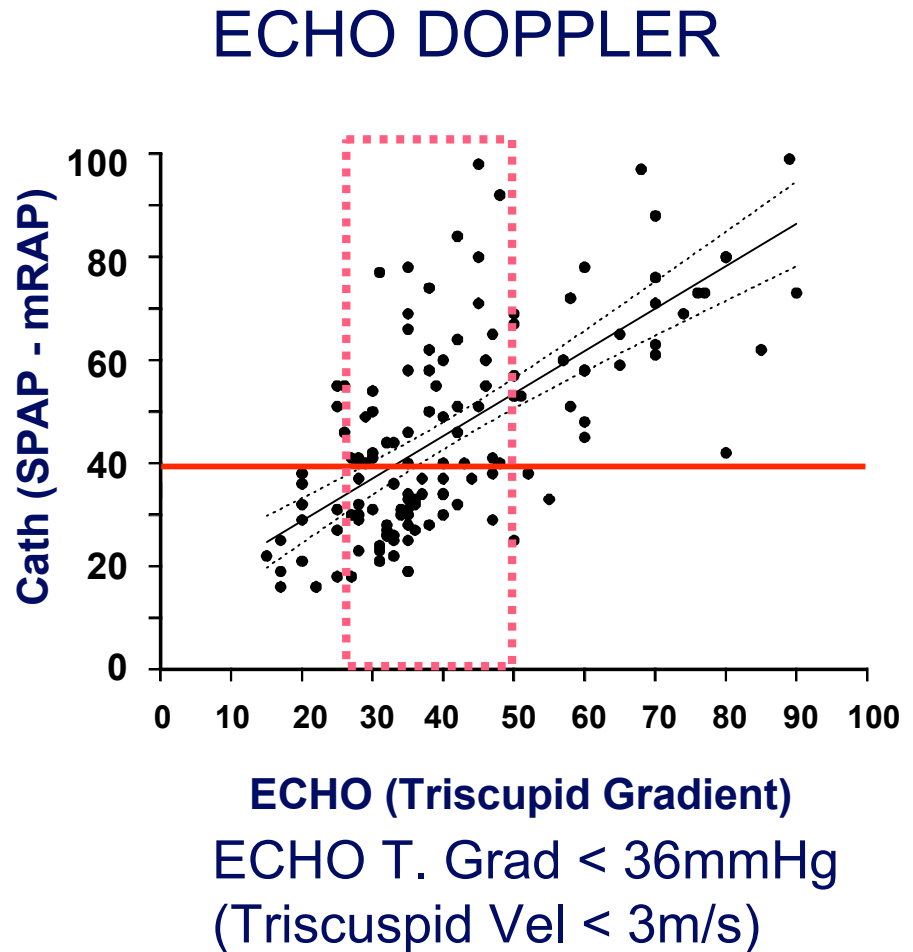
Predicting pulmonary hypertension from gas transfer in SSc



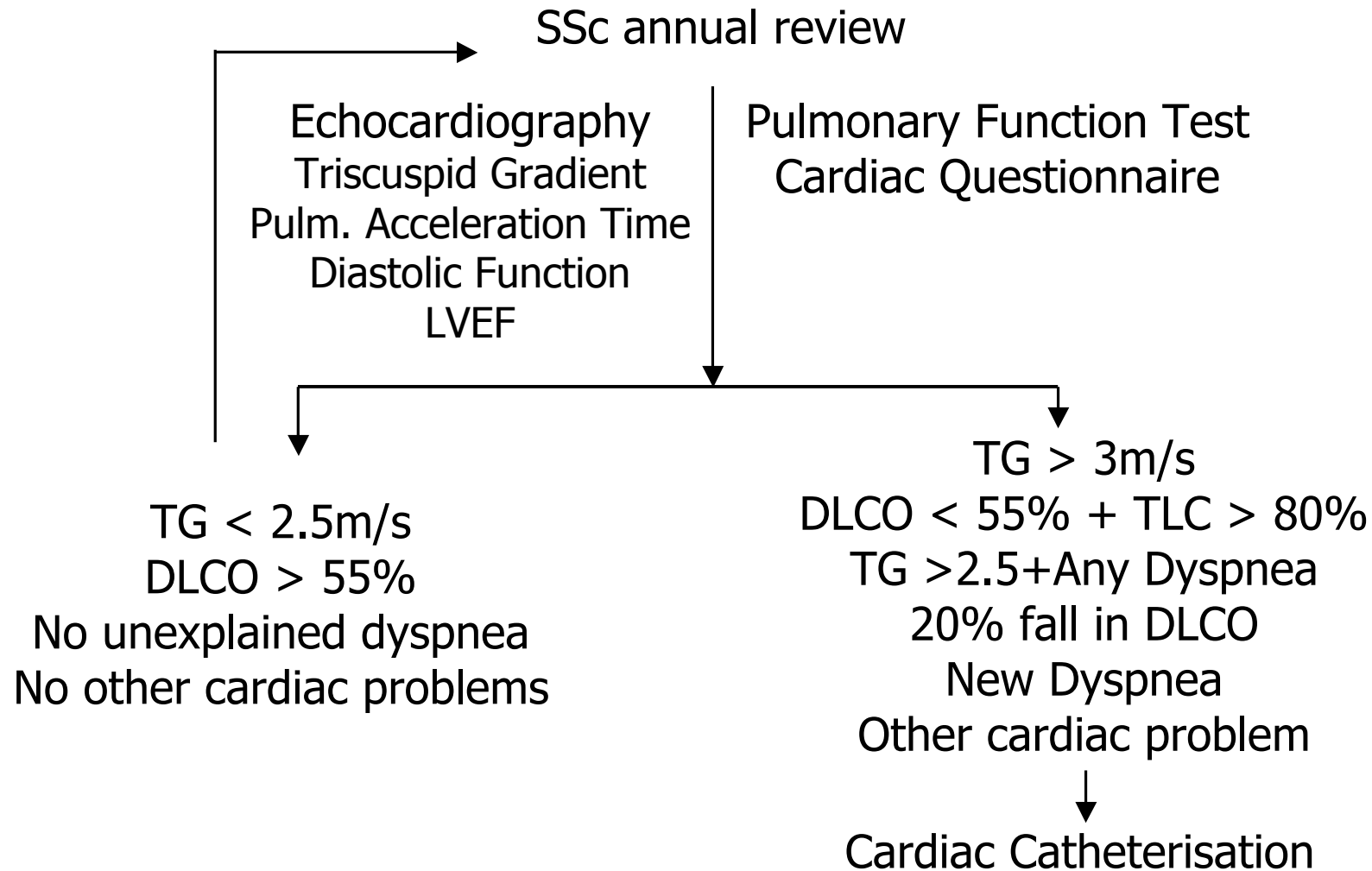
Mukerjee, et al. *Rheumatology* 2004

Doppler-PASP as a screening tool for PAH-SSc

- ◆ PAH = mPAP > 25mmHg and PCW < 15mmHg
 - Screening echo estimates SPAP only
 - mPAP approximates to 0.6 x SPAP
 - mPAP 25mmHg = TV of 3.1m/s or SPAP 40mmHg ?



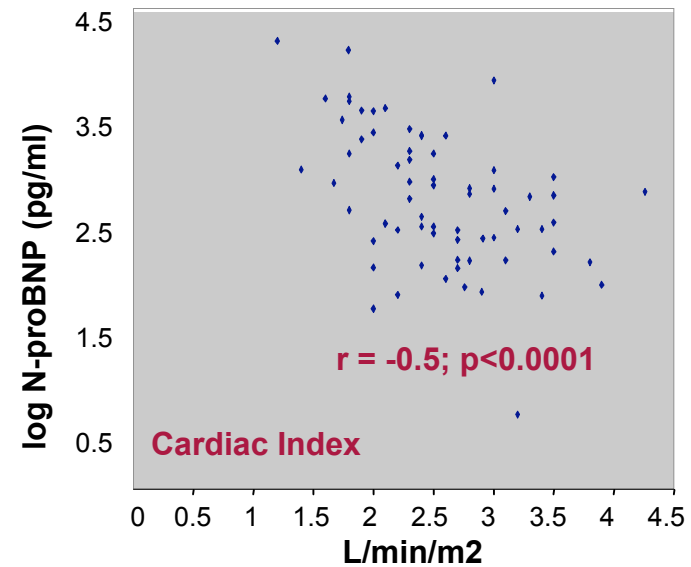
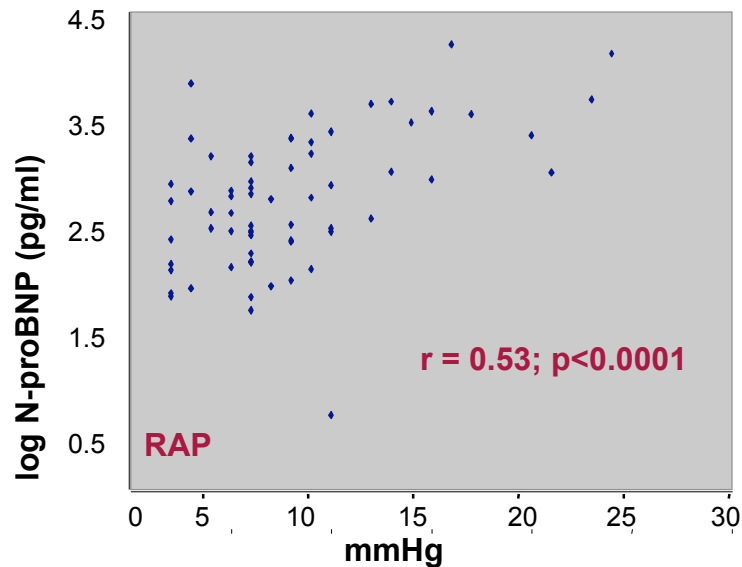
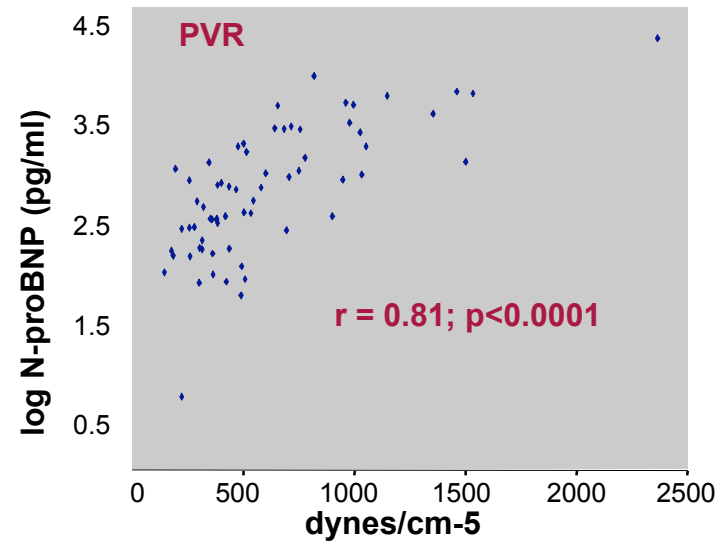
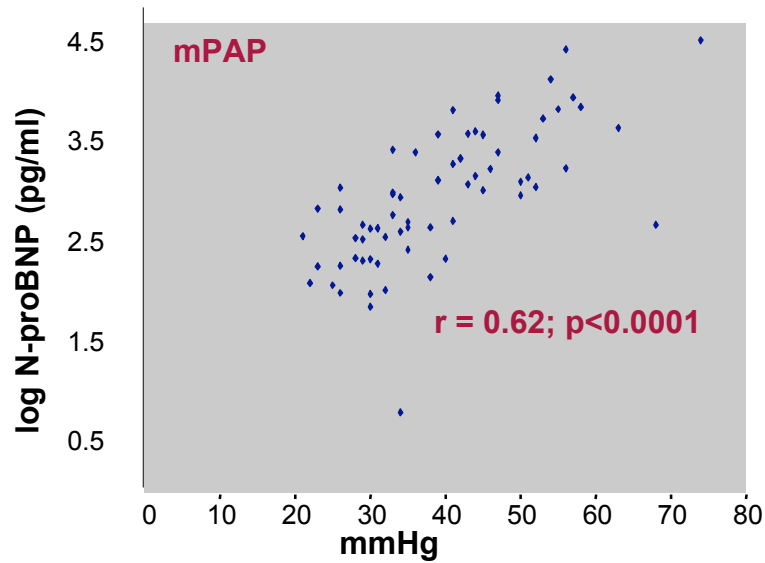
RFH Screening Algorithm



Prognostic value of N-terminal pro-BNP in PAH-SSc

- ◆ NT-pro-BNP measured in 41 patients with definite SSc (normal PAP by echo and RHC, n=11) and 68 with elevated PAP (by RHC)
- ◆ 3 monthly follow-up NT-pro-BNP in 52 subjects with SSc-PAH
- ◆ Outcome measures:
 - Correlation of baseline NT-pro-BNP with clinical and haemodynamic variables
 - Association of elevated NT-pro-BNP with survival
 - Relationship between change in NT-pro-BNP and survival
- ◆ Exclusions:
 - Renal impairment (serum creatinine > 150uM)
 - LV impaired function
 - Reduced LVEF (Echo) or elevated PCWP at catheterisation

Correlation of plasma NT-proBNP levels with cardiopulmonary haemodynamics (mPAP, PVR, RAP and CI)



Predictors of survival SSc-PAH

Univariate analysis of CI, mPAP, RAP, SVO₂, WHO class, age SSc type, NT-BNP, Δ NT-BNP, 6MWD & gender

Variable		Hazard Ratio	Confidence Interval	<i>p</i> value
NT-BNP	log ₁₀ ⁺	2.57	0.9-7.4	0.08
ΔNT-BNP	log₁₀⁺	4.7	1.2-19.5	0.035
Gender	Male	4.4	1.6-12.5	0.01
6-MWD	100m+	0.69	0.4-1.1	0.12

EARLY intervention in SSc-PAH

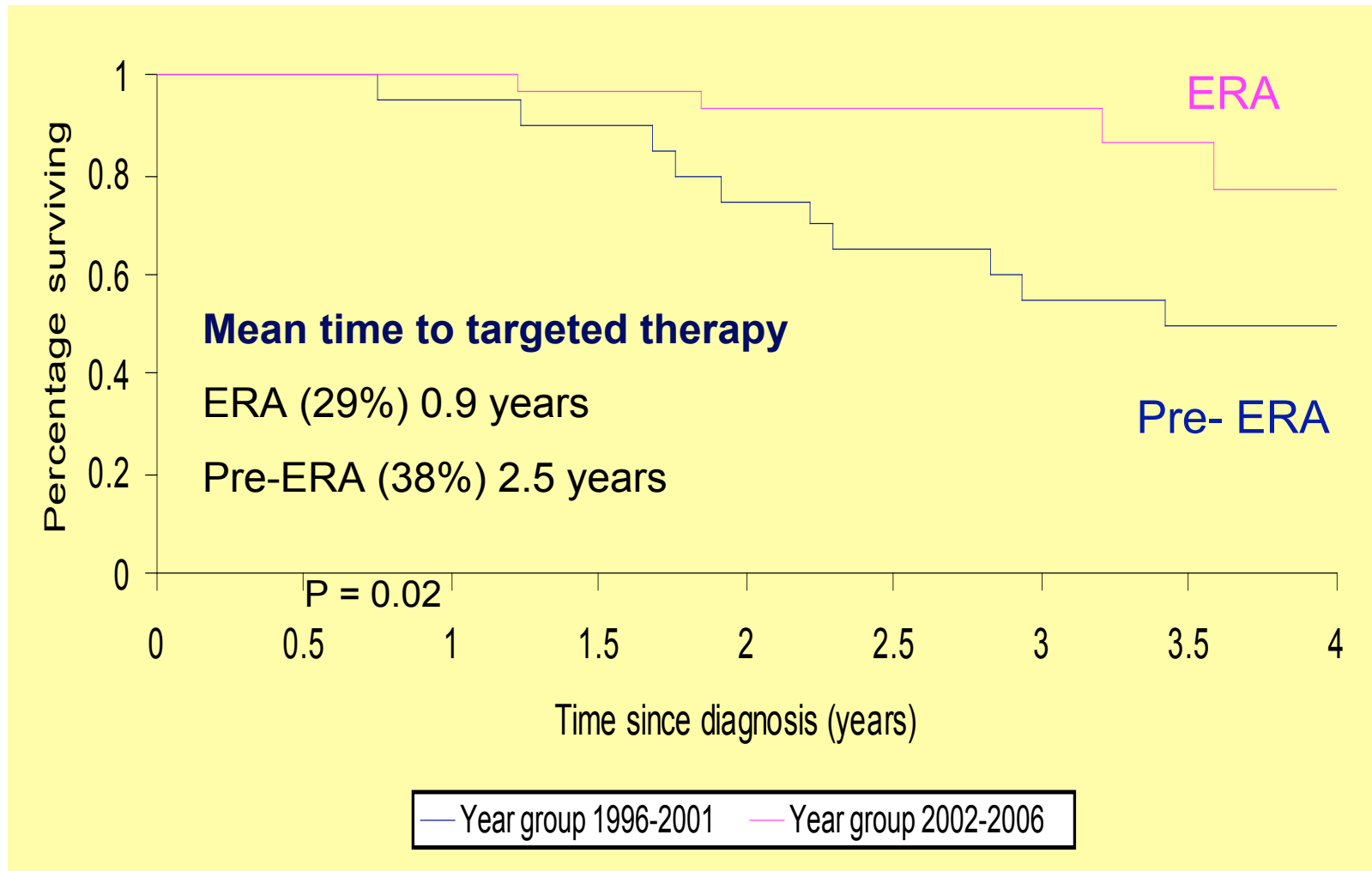
- ◆ 56 SSc-PAH patients (1996 - 2006),
Functional Class I or II without significant pulmonary fibrosis
- ◆ PAH : mPAP > 25 mmHg at rest or 30mmHg (with exercise) and PCW < 15 mmHg on RHC
- ◆ No significant lung fibrosis
 - $\leq 1/3$ involvement on HRCT
 - FVC $\geq 70\%$
- ◆ Survival at 4 years before and after 2002 compared

Demographics of early PAH-SSc

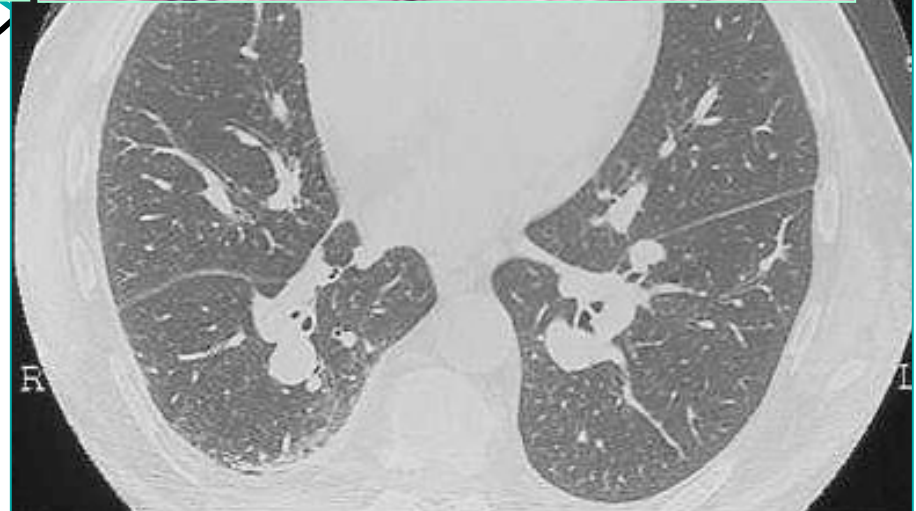
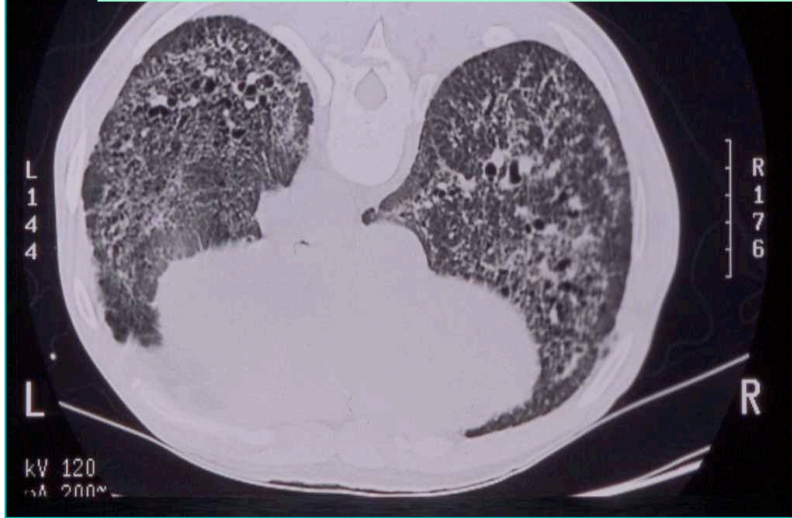
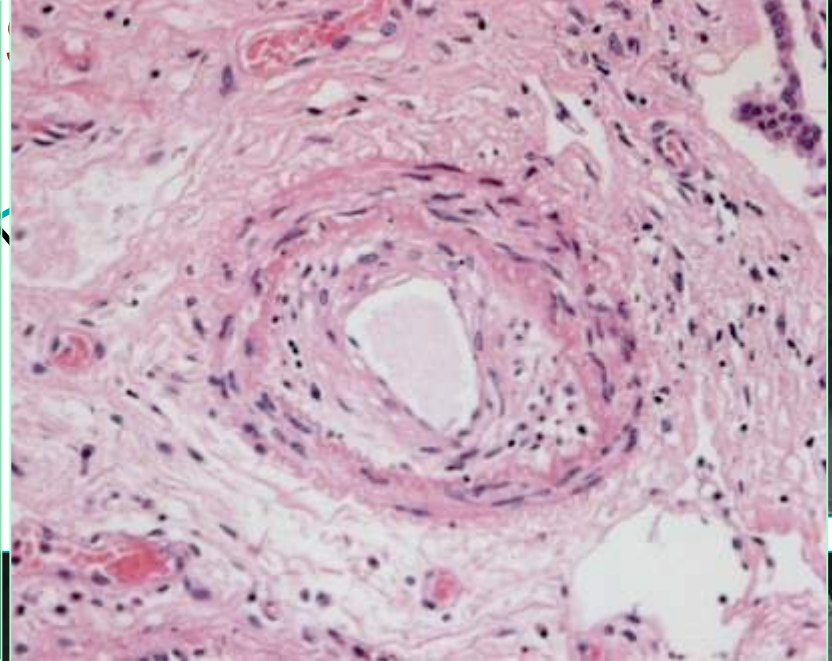
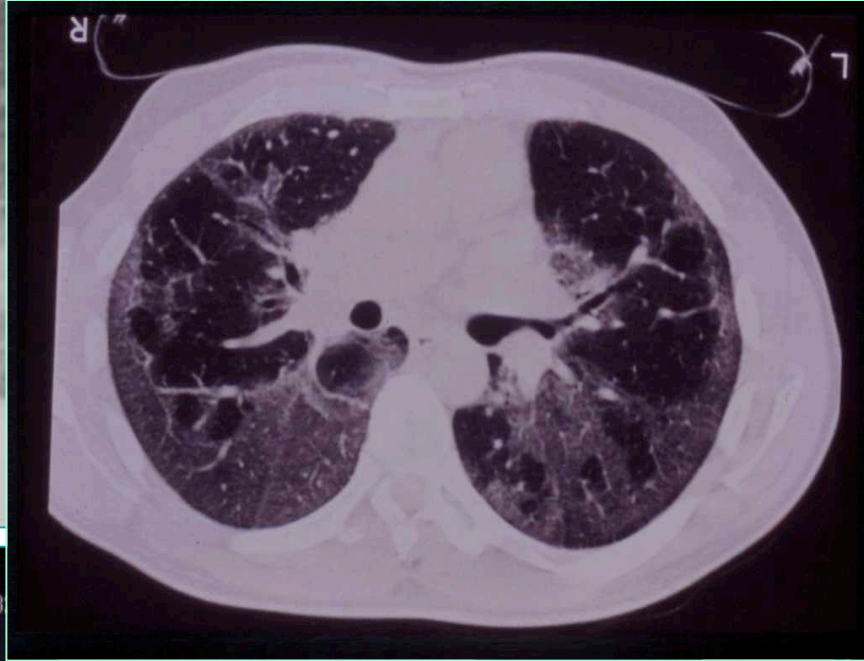
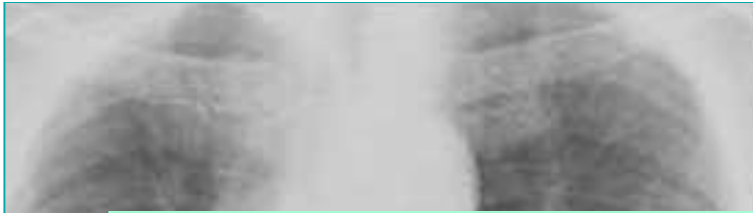
	1996 – 2001 (n= 21)	2002 - 2006 (n= 35)
Mean age (yrs)	64	59
Sex (M/F)	3/18	8/27
mPAP (mmHg) [range]	32 (25 – 47)	34 (25 - 64)
RAP (mmHg)	5	5
PCW (mmHg)	9	10
PVR (dynes/sec/cm-5)	338	367
lcSSc	95%	94%
dcSSc	5%	0%
Overlap SSc	0%	6%

Royal Free Cohort – Kabunga et al, 2007

Survival in PAH-SSc diagnosed at Functional Class I or II has improved



monary c



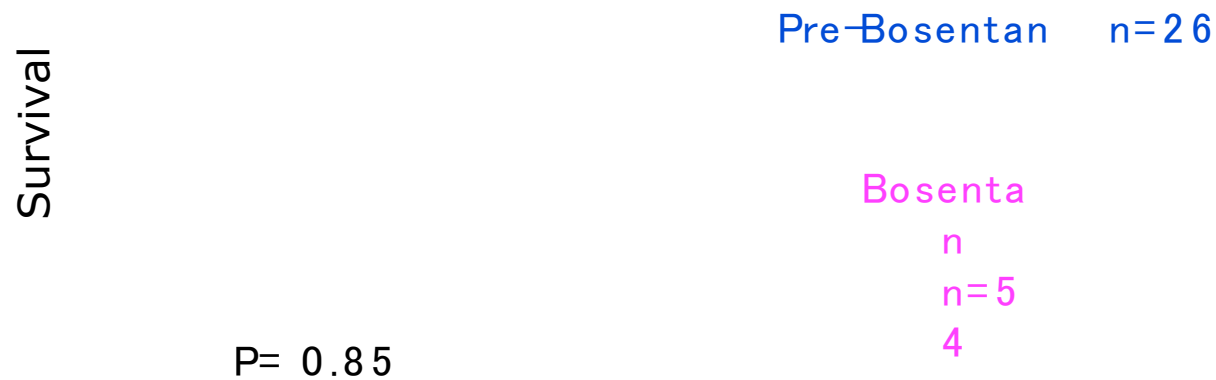
Does ERA therapy improve outcome in pulmonary fibrosis associated SSc-PH?

- ◆ PH : mPAP $>$ 25 mmHg at rest or 30mmHg (with exercise) and PCW $<$ 15 mmHg on right heart catheterisation
- ◆ PF: \geq 1/3 involvement on HRCT, Forced Vital Capacity (FVC) \leq 70%
- ◆ Assessment of the impact of ERA therapy on survival of patients with fibrosis associated SSc-PH versus historical controls

Does first-line ERA therapy benefit fibrosis associated PH in SSc?

- ◆ 305 SSc-PAH patients (1996 - 2006)
- ◆ 225 patients with isolated SSc-PAH
- ◆ 80 patients with fibrosis associated SSc-PH (26 patients before 2002)
- ◆ 65% treated with first line bosentan post-2002

Fibrosis associated SSc-PH: impact of oral therapies on survival



Conclusions

- ◆ Cardio-respiratory complications are the major cause of SSc-related death
- ◆ PAH is a major complication of SSc and screening is mandatory
- ◆ Serum NT-pro-BNP is helpful in monitoring and may have potential for screening
- ◆ Advanced therapies are effective in PAH-SSc
- ◆ Outcome in PAH-SSc is worse than iPAH
- ◆ Co-existent lung fibrosis worsens outcome and may blunt treatment response in PAH-SSc