ΔΙΑΓΝΩΣΤΙΚΟΣ ΚΑΙ ΘΕΡΑΠΕΥΤΙΚΟΣ ΑΛΓΟΡΙΘΜΟΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ ΚΑΙ ΡΕΥΜΑΤΙΚΑ ΝΟΣΗΜΑΤΑ

ΘΕΟΔΩΡΟΣ ΔΗΜΗΤΡΟΥΛΑΣ

ΕΠΙΚΟΥΡΟΣ ΚΑΘΗΓΗΤΗΣ ΡΕΥΜΑΤΟΛΟΓΙΑΣ
ΑΠΘ

Σύγκρουση συμφερόντων

Παρούσα παρουσίαση: ΚΑΜΙΑ

Honoraria for lectures and/or consultancy from Abbvie, Actelion, Enorasis, Elpen, BMS, Jansen, MSD, Genesis Pharma, Hospital Line, Novartis, UCB, Pfizer UK/Greece, Roche, Sanofi, Lilly

Haemodynamic definitions of pulmonary hypertension

Definition	Characteristics*	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]	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP - mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

[a]All values measured at rest; see also section 7.
[b]According to Table 4.
[c]Wood Units are preferred to dynes.s.cm^{-5}.

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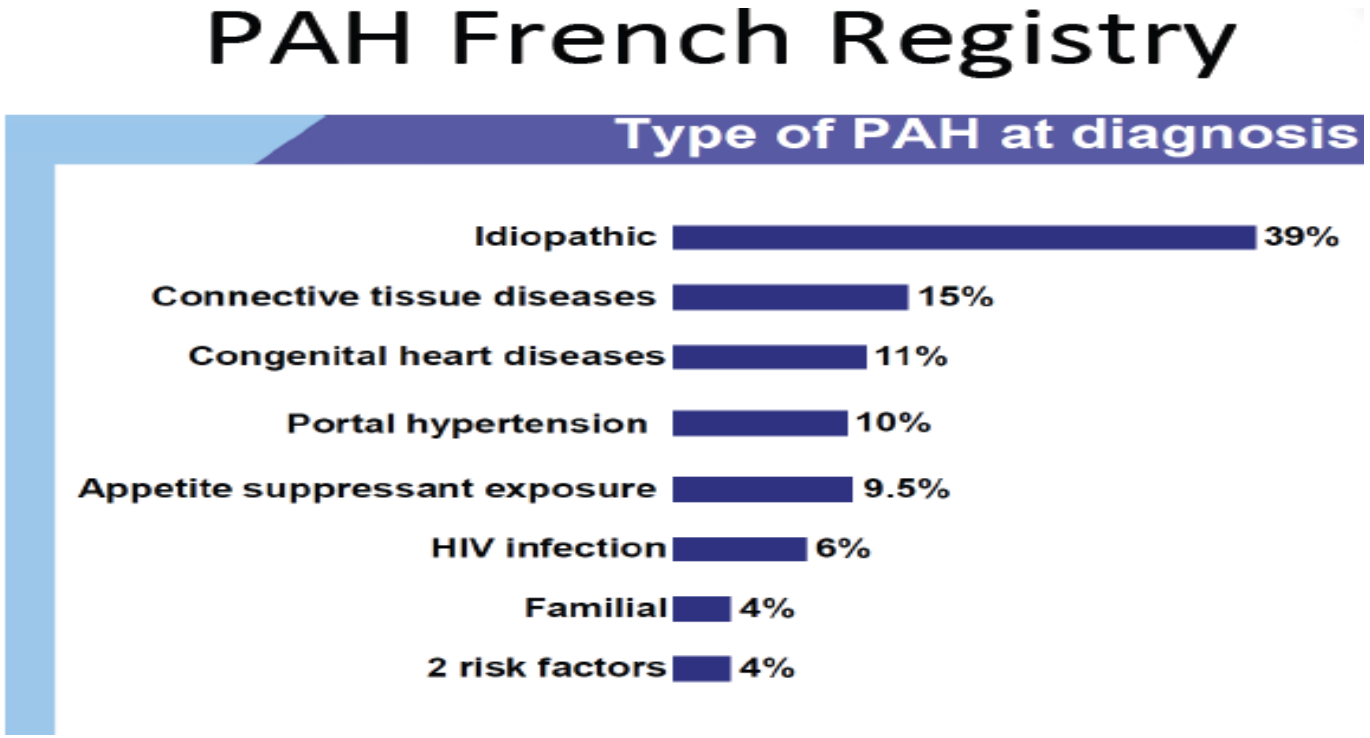
www.escardio.org

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

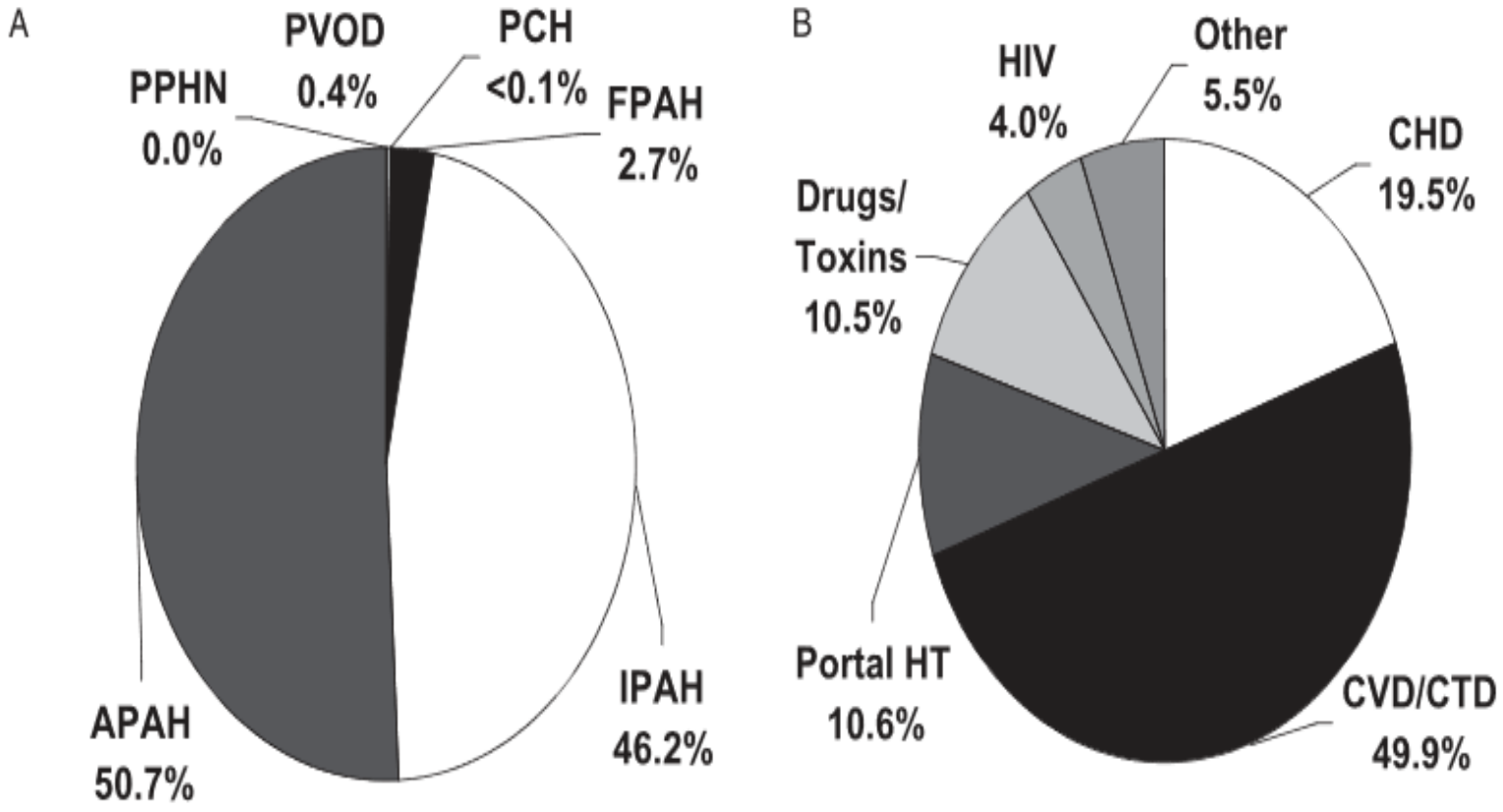
Η CTD -PAH ΑΠΟΤΕΛΕΙ ΤΗ 2Η ΣΥΧΝΟΤΕΡΗ ΑΙΤΙΑ ΜΕΤΑ ΤΗΝ ΙΔΙΟΠΑΘΗ PAH



Humbert M et al, Am J Respir Crit Care Med 2006

Η CTD -PAH ΑΠΟΤΕΛΕΙ ΤΗ 2^{Η} ΣΥΧΝΟΤΕΡΗ ΑΙΤΙΑ ΜΕΤΑ ΤΗΝ ΙΔΙΟΠΑΘΗ PAH

REVEAL REGISTRY



David B. Badesch et al, Chest 2010; 137(2):376–387

CHEST

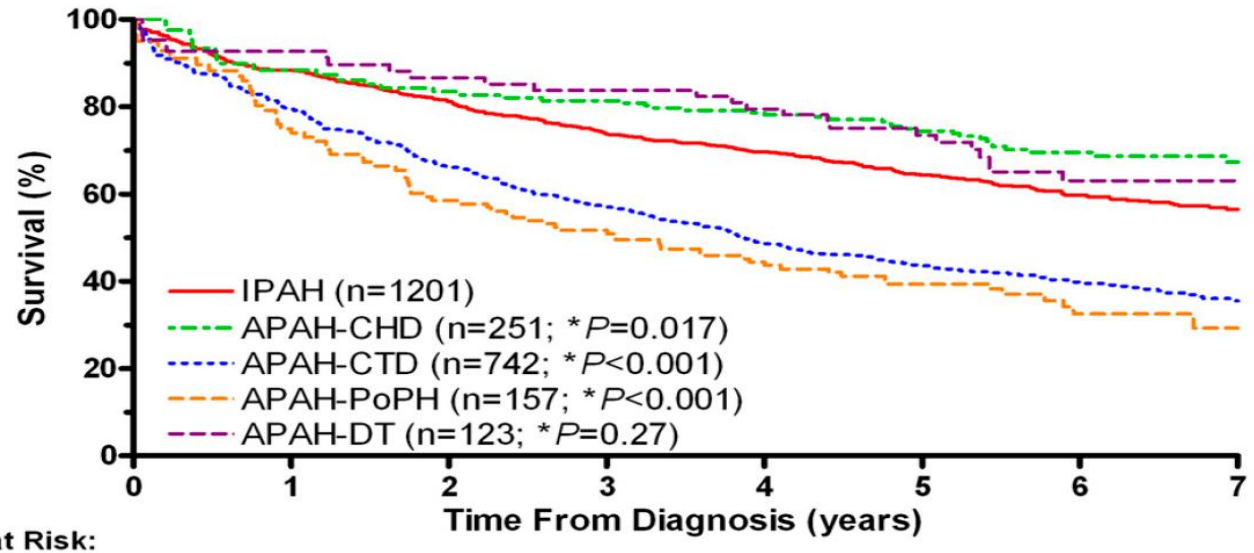
Original Research

PULMONARY VASCULAR DISEASE

An Evaluation of Long-term Survival From Time of Diagnosis in Pulmonary Arterial Hypertension From the REVEAL Registry

Raymond L. Benza, MD; Dave P. Miller, MS; Robyn J. Barst, MD, FCCP; David B. Badesch, MD, FCCP; Adaani E. Frost, MD, FCCP; and Michael D. McGoon, MD, FCCP

A



No. at Risk:								
IPAH	415	553	600	609	538	415	268	143
APAH-CHD	46	70	107	144	150	138	85	49
APAH-CTD	257	342	344	329	276	203	138	67
APAH-PoPH	56	74	70	72	59	42	20	8
APAH-DT	40	57	62	60	55	45	29	21

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http://dx.doi.org/10.1016/j.jacc.2013.10.029

Updated Clinical Classification of Pulmonary Hypertension

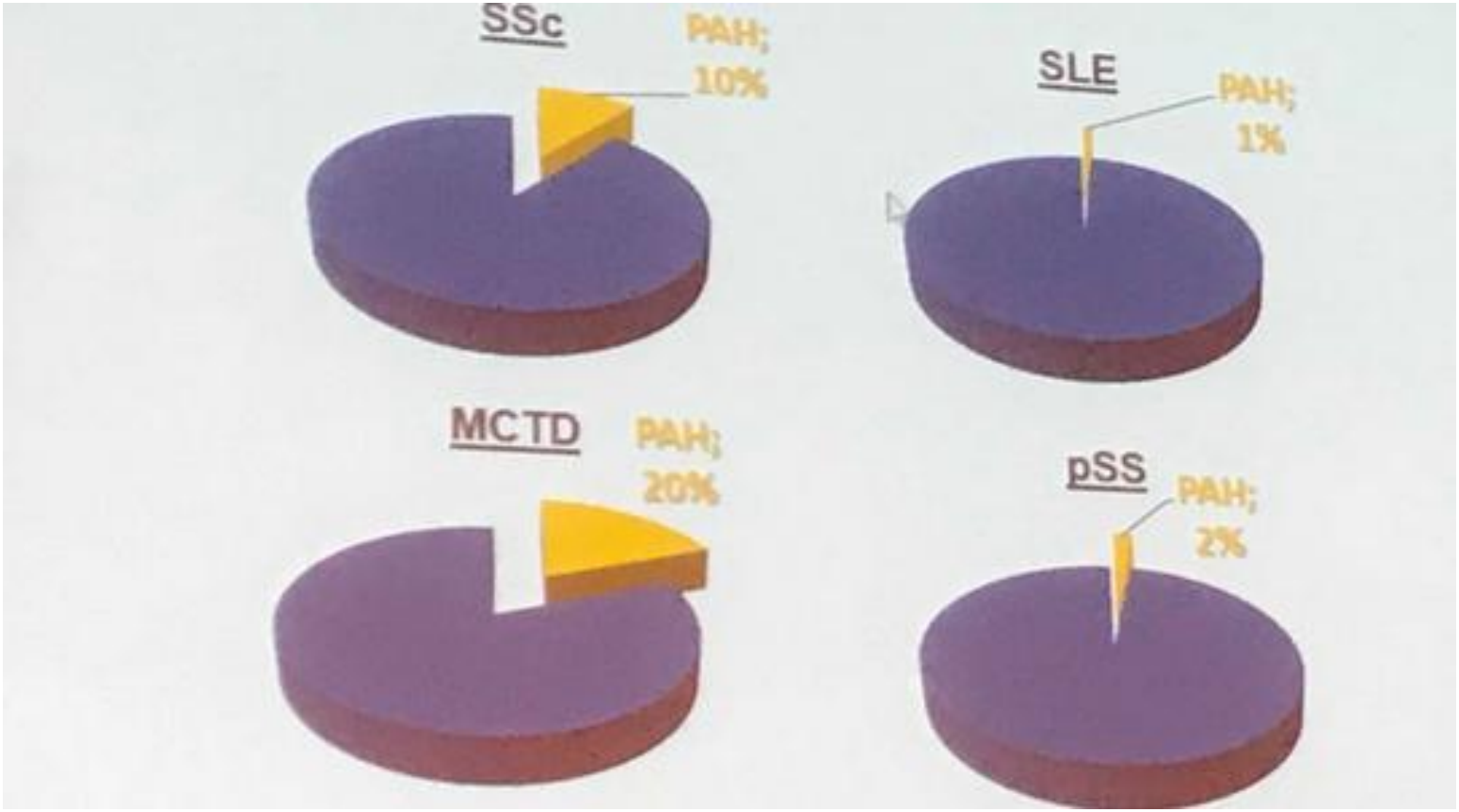
Gerald Simonneau, MD,* Michael A. Gatzoulis, MD, PHD,† Ian Adatia, MD,‡ David Celermajer, MD, PHD,§ Chris Denton, MD, PHD,‖ Ardeschir Ghofrani, MD,¶ Miguel Angel Gomez Sanchez, MD,# R. Krishna Kumar, MD,** Michael Landzberg, MD,†† Roberto F. Machado, MD,‡‡ Horst Olschewski, MD,§§ Ivan M. Robbins, MD,‖‖ Rogiero Souza, MD, PHD¶¶

Le Kremlin–Bicêtre and Paris, France; London, United Kingdom; Edmonton, Alberta, Canada; Sydney, Australia; Marburg, Germany; Madrid, Spain; Kerala, India; Boston, Massachusetts; Chicago, Illinois; Graz, Austria; Nashville, Tennessee; and São Paulo, Brazil

ΟΜΑΔΑ I	**ΠΝΕΥΜΟΝΙΚΗ ΑΡΤΗΡΙΑΚΗ ΥΠΕΡΤΑΣΗ** 1. Ιδιοπαθής ΠΑΥ 2. Οικογενής 3. Σχετιζόμενη με a) Ρευματικά νοσήματα b) Συγγενείς διαφυγές από συστηματική προς πνευμονική κυκλοφορία c) Πυλαία υπέρταση d) Λοίμωξη HIV e) Φάρμακα και τοξίνες f) Άλλα αίτια (παθήσεις θυρεοειδούς, νόσος Gaucher, αιμοσφαιρινοπάθειες, μυελοϋπερπλαστικές διαταραχές, σπληνεκτομή) 4. Σχετιζόμενη με σημαντική συμμετοχή φλεβών ή τριχοειδών a) Πνευμονική φλεβοαποφρακτική νόσος b) Πνευμονική τριχοειδική αιμαγγειωμάτωση c) Επιμένουσα πνευμονική υπέρταση των νεογνών
ΟΜΑΔΑ II	**ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ ΜΕ ΑΡΙΣΤΕΡΗ ΚΑΡΔΙΟΠΑΘΕΙΑ** 1. Παθήσεις του αριστερού κόλπου ή της αριστερής κοιλίας 2. Βαλβιδοπάθειες των αριστερών καρδιακών κοιλοτήτων
ΟΜΑΔΑ III	**ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ ΣΧΕΤΙΖΟΜΕΝΗ ΜΕ ΠΝΕΥΜΟΝΟΠΑΘΕΙΕΣ Ή/ΚΑΙ ΥΠΟΞΑΙΜΙΑ** 1. Χρόνια αποφρακτική πνευμονοπάθεια 2. Διάμεση πνευμονοπάθεια 3. Δύσπνοια ύπνου 4. Διαταραχές κυψελιδικού αερισμού 5. Χρόνια έκθεση σε μεγάλο υψόμετρο 6. Διαταραχές της ανάπτυξης
ΟΜΑΔΑ IV	**ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ ΟΦΕΙΛΟΜΕΝΗ ΣΕ ΧΡΟΝΙΑ ΘΡΟΜΒΩΤΙΚΗ Ή/ΚΑΙ ΕΜΒΟΛΙΚΗ ΝΟΣΟ** 1. Θρομβοεμβολική απόφραξη εγγύς κλάδων των πνευμονικών αρτηριών 2. Θρομβοεμβολική απόφραξη περιφερικών κλάδων των πνευμονικών αρτηριών 3. Μη θρομβογενής πνευμονική εμβολή (όγκοι, παράσιτα, ξένα σώματα)
ΟΜΑΔΑ V	**ΠΟΙΚΙΛΑ** Σαρκοείδωση, ιστιοκύττωση Χ, λεμφαγγειωμάτωση, συμπίεση των πνευμονικών αγγείων (αδενοπάθεια, όγκος, ινωτική μεσοθωρακίτιδα)

ΠΑΥ ΣΤΑ ΡΕΥΜΑΤΙΚΑ ΝΟΣΗΜΑΤΑ

- Η συχνότητα της ΠΑΥ ποικίλει ανάλογα με το νόσημα
- Η ΠΑΥ σε ασθενείς με σκληρόδερμα αποτελεί την καλύτερα μελετημένη ομάδα ασθενών με συστηματικά νοσήματα
- Χρειάζονται επιδημιολογικές μελέτες για την καλύτερη κατανόηση της ΠΑΥ στα υπόλοιπα συστηματικά νοσήματα



Shahane A. **Rheumatol Int**. 2013 Jul;33(7):1655-67.

ΣΚΛΗΡΟΔΕΡΜΑ ΚΑΙ ΠΝΕΥΜΟΝΙΚΗ ΑΡΤΗΡΙΑΚΗ ΥΠΕΡΤΑΣΗ (SScPAH)

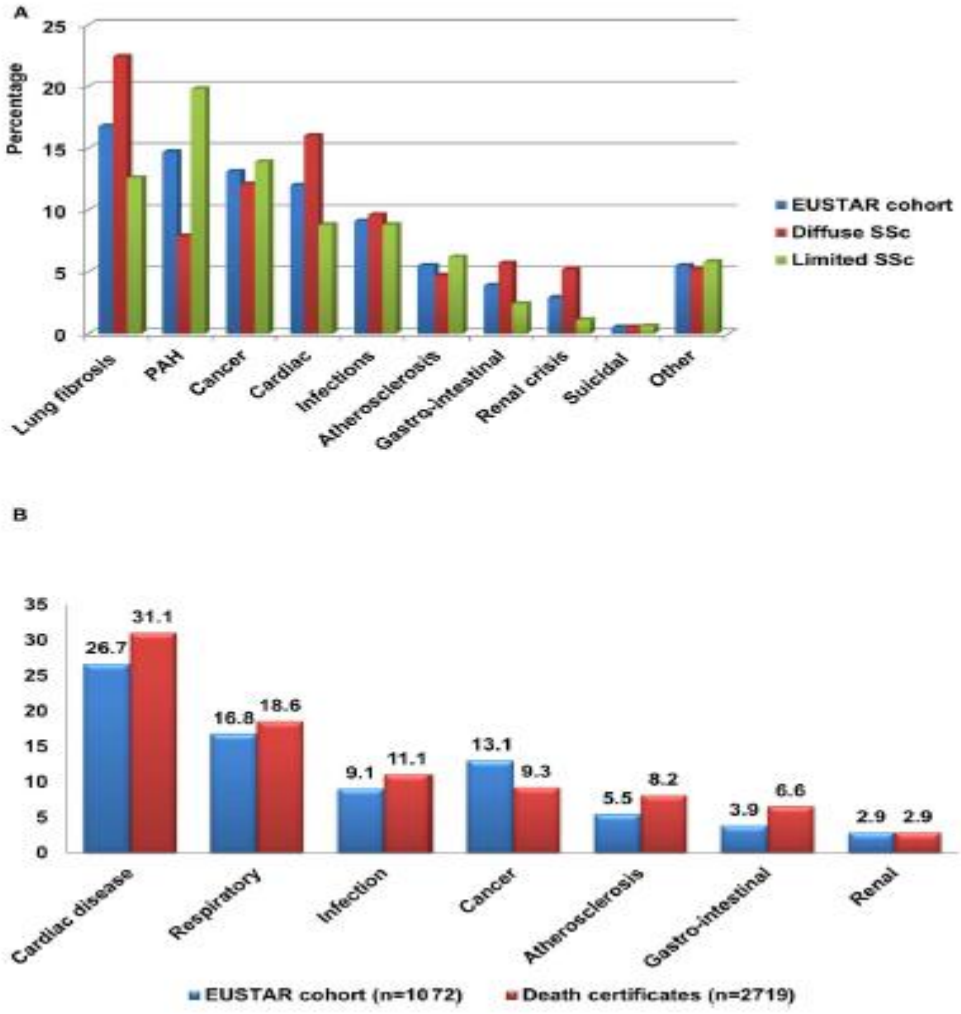
Reference	Methodology	Diagnosis	PAH prevalence
Mukerjee; 2003, UK	• *n* = 722, single center • Prospective 1998-2002	RHC	12%
Hachulla; 2005, France	• *n* = 599, multi-center • Prospective, cross sectional	RHC	8%
Phung; 2009, Australia	• *n* = 184, single center • Prospective, cross sectional	RHC	13%
DETECT study; 2013 International	• *n* = 646, multicenter • Prospective, cross sectional	RHC	19%
Avouac; 2010	• ~ 5000 patients • metaanalysis	RHC	6-9%

Mukerjee D, et al. Ann Rheum Dis 2003
Hachulla E, et al. Arthritis Rheum 2005
Phung S, et al. Intern Med J 2009
Coghlan G, et al. Ann Rheum Dis 2013
Avouac J et al, J Rheumatol 2010

Annals of the
Rheumatic Diseases

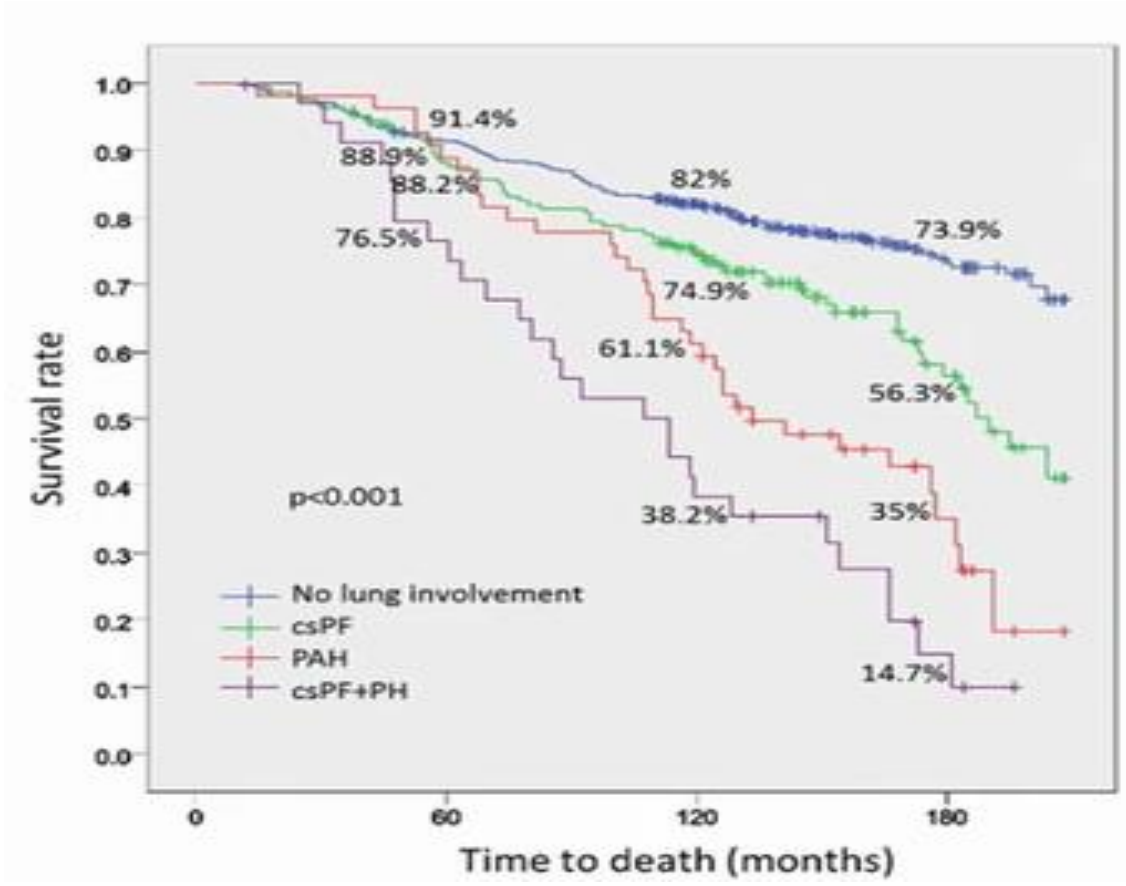
Mapping and predicting mortality from systemic sclerosis

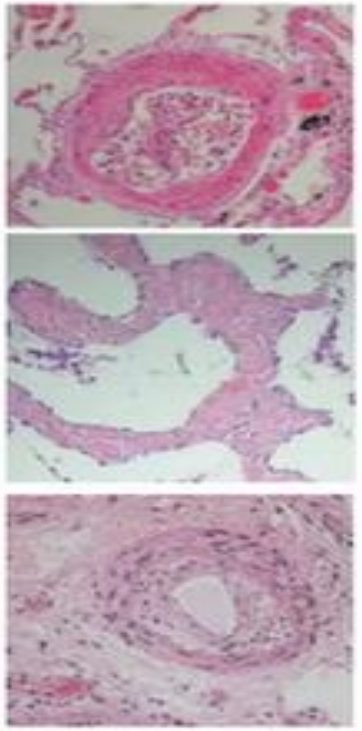
Elhai M, *et al. Ann Rheum Dis* 2017;**76**:1897–1905.



Η ΠΝΕΥΜΟΝΙΚΗ ΠΡΟΣΒΟΛΗ ΑΠΟΤΕΛΕΙ ΔΥΣΜΕΝΗ ΠΡΟΓΝΩΣΤΙΚΟ ΠΑΡΑΓΟΝΤΑ

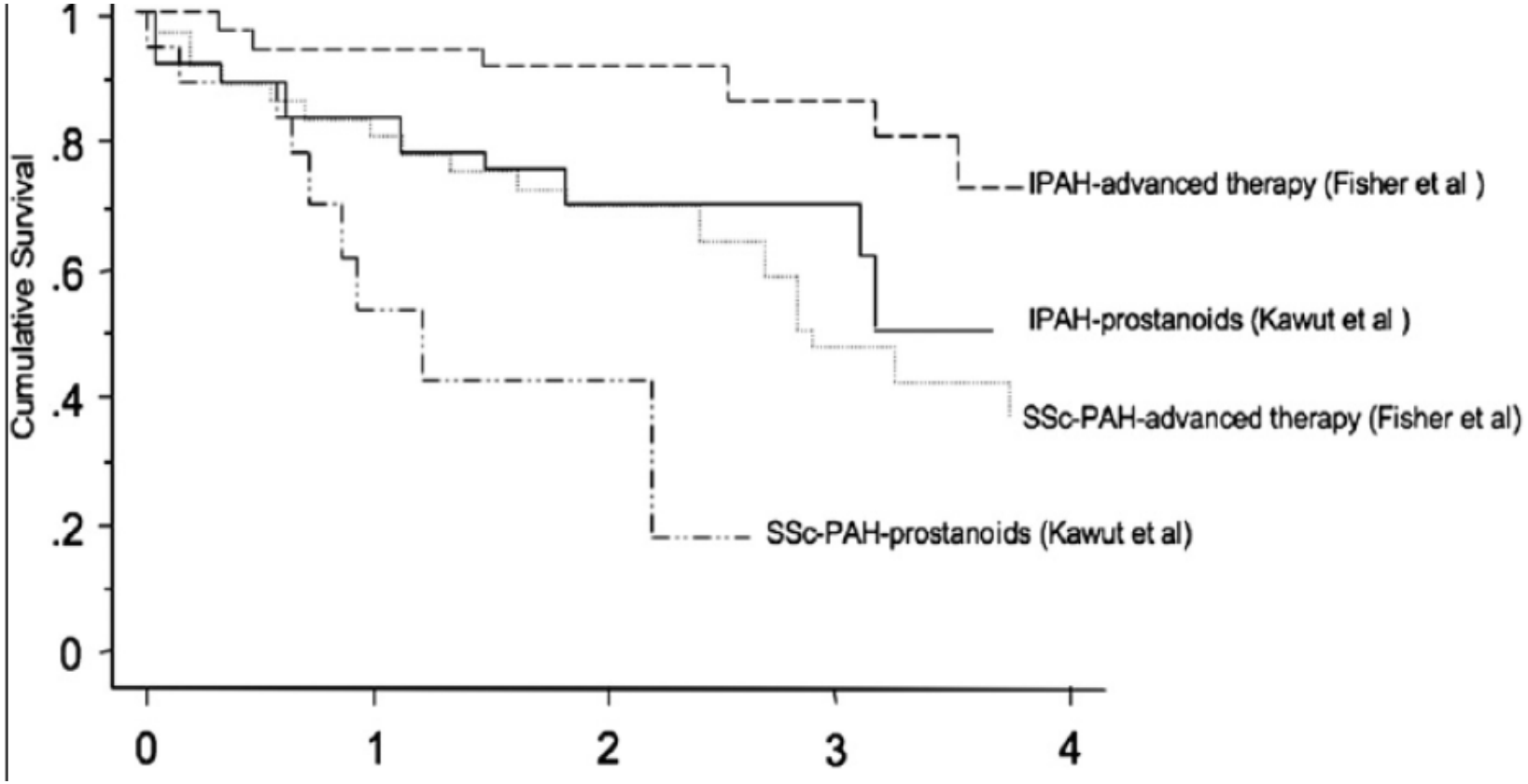
677 consecutive SSc patients, followed up for up to 15 years





Nihtyanova et al, Arthritis Rheumatol 2014

Η ΠΡΟΓΝΩΣΗ ΤΗΣ SScPAH ΕΙΝΑΙ ΧΕΙΡΟΤΕΡΗ ΑΠΟ ΑΥΤΗ ΤΗΣ IPAH

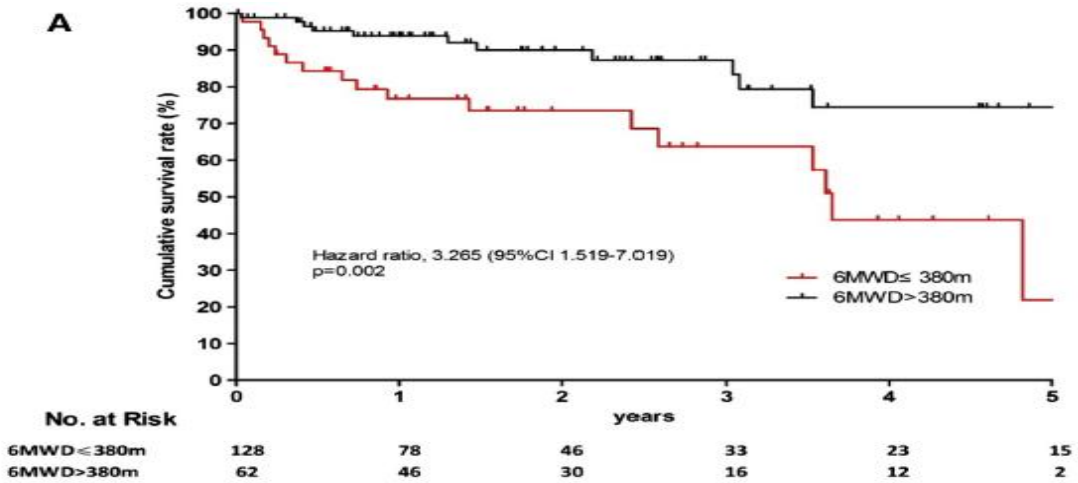


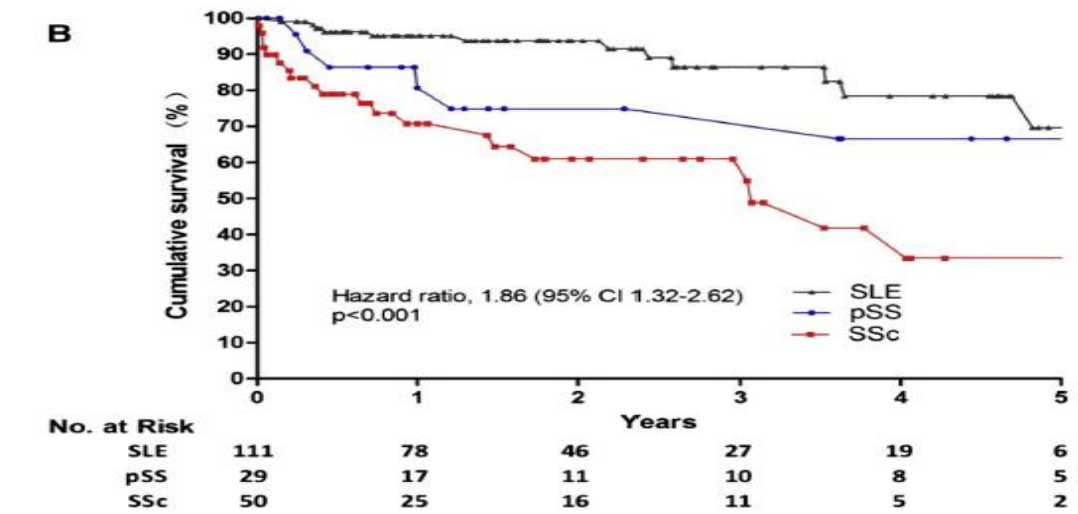
Kawut et al, Chest 2003
Fisher et al, Arthritis Rheum 2006
Le Pavec et al Am J Respir Crit Care Med 2010

Clinical characteristics and survival of pulmonary arterial hypertension associated with three major connective tissue diseases: A cohort study in China

Jiuliang Zhao [a,1], Qian Wang [a,1], Yongtai Liu [b,1], Zhuang Tian [b], Xiaoxiao Guo [b], Hui Wang [b], Jinzhi Lai [b], Can Huang [a], Xiaoxi Yang [a], Mengtao Li [a,*], Xiaofeng Zeng [a,*]

Int J Cardiol. 2017 Jun 1;236:432-437.





Η ΠΡΟΓΝΩΣΗ ΤΗΣ ΠΑΥ ΣΤΟ ΣΚΛΗΡΟΔΕΡΜΑ ΕΙΝΑΙ ΧΕΙΡΟΤΕΡΗ ΑΠΟ ΤΑ ΑΛΛΑ ΣΥΣΤΗΜΑΤΙΚΗ ΝΟΣΗΜΑΤΑ

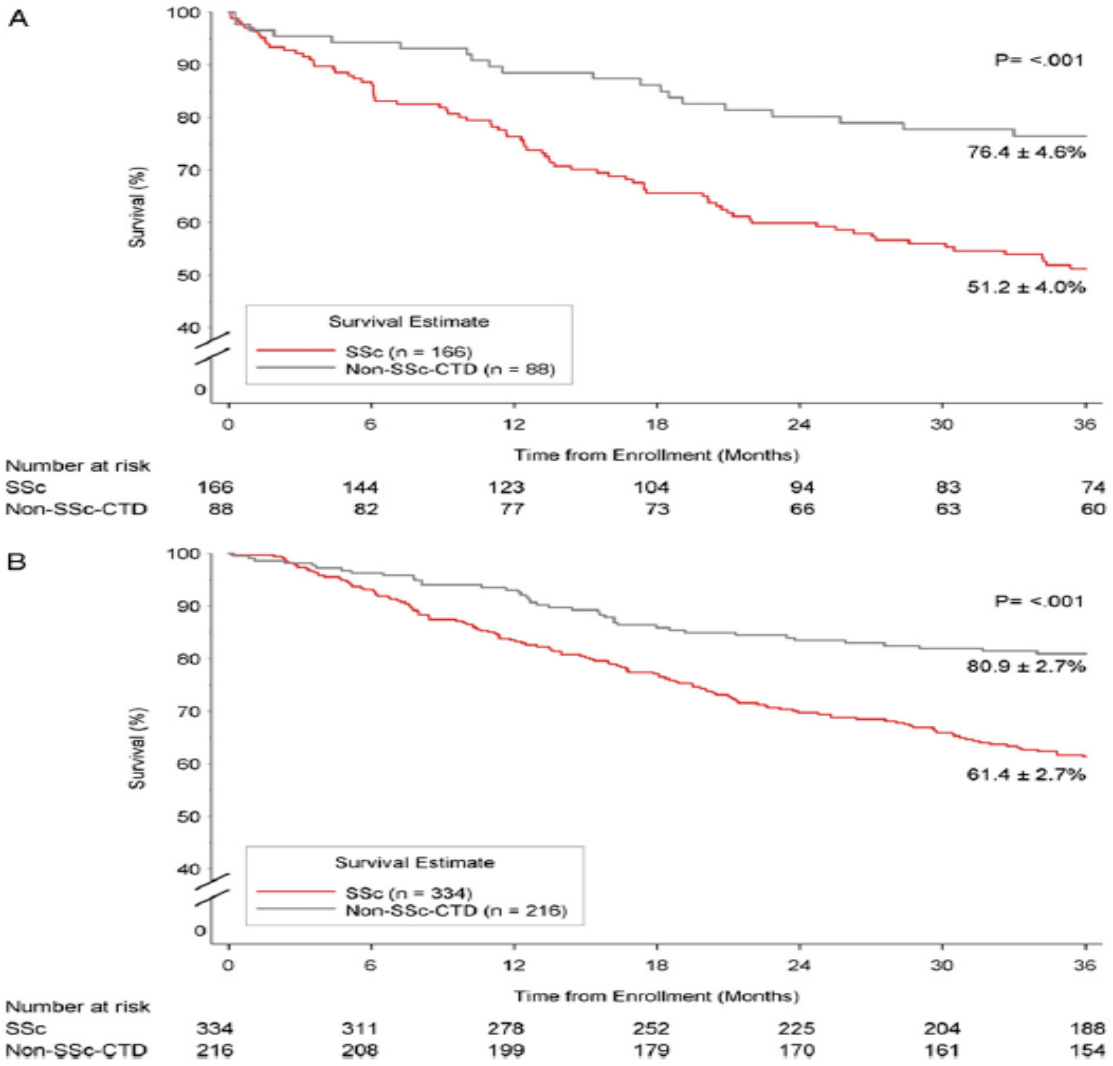
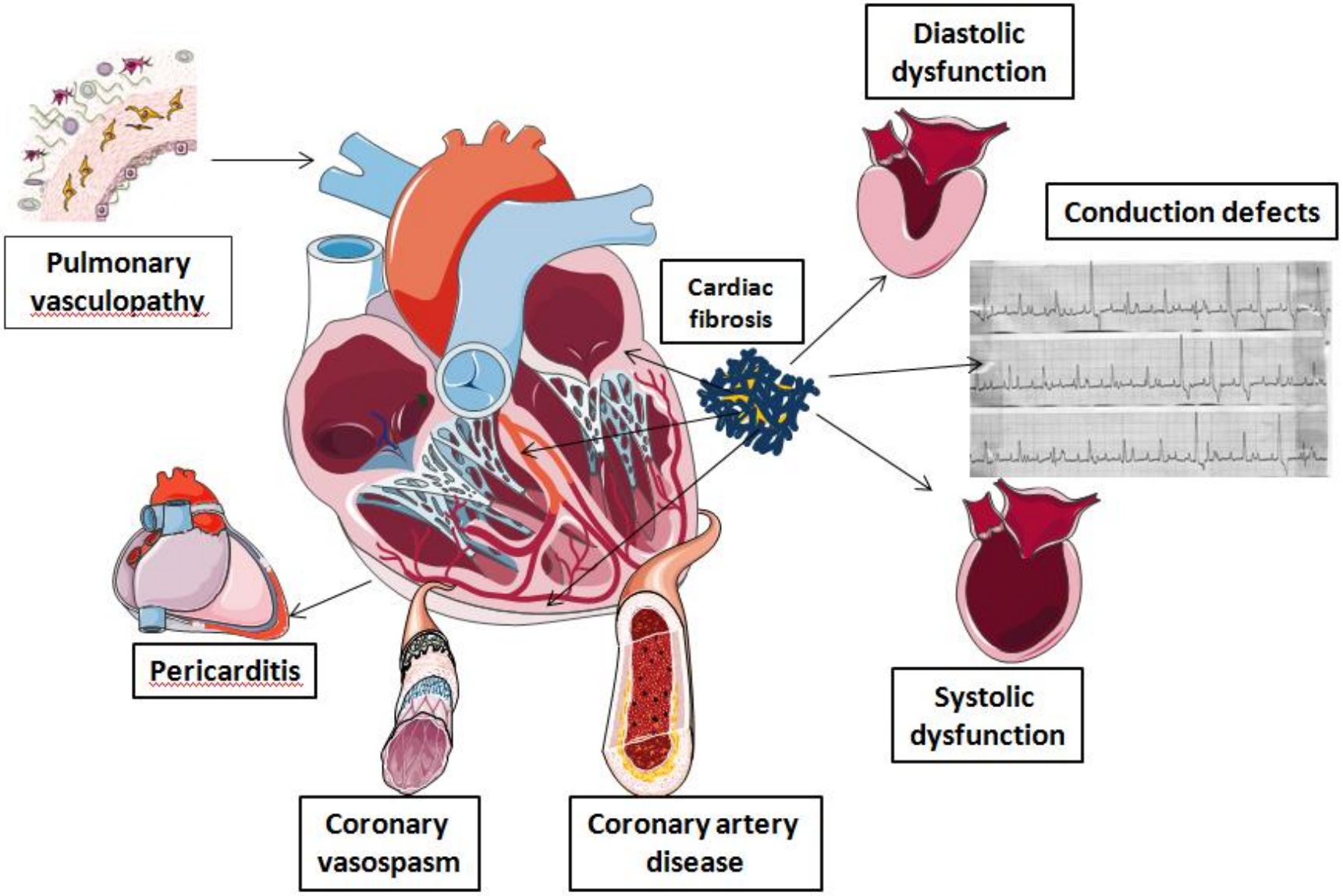


Figure 2 – *Three-year survival curves in patients with SSc and non-SSc-CTD-APAH. A, Three-year survival from enrollment in the newly diagnosed SSc group was 51.2% ± 4.0% compared with 76.4% ± 4.6% in the non-SSc-CTD group (P < .001). B, Three-year survival from enrollment in the previously diagnosed SSc group was 61.4% ± 2.7% compared with 80.9% ± 2.7% in the non-SSc-CTD group (P < .001). See Figure 1 legend for expansion of abbreviations.*

↓ DLCO

↑ NT-proBNP

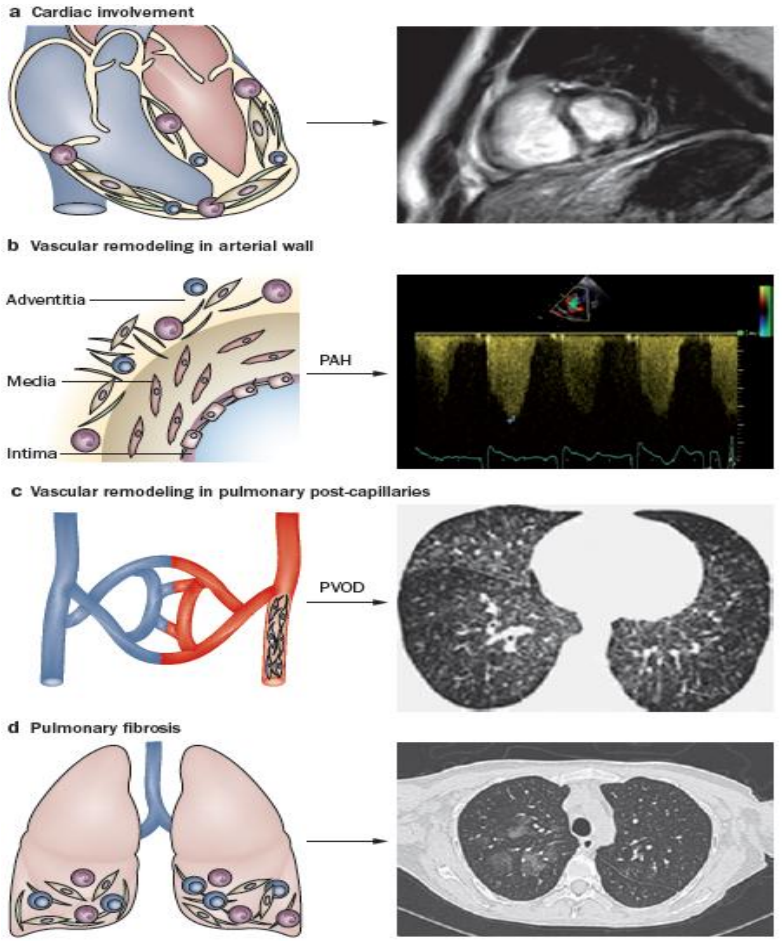
Chung et al,Chest. 2014 Dec; 146(6): 1494–1504.



Dimitroulas et al, Curr Pharm Des 2013

ΜΟΝΑΔΙΚΟΣ ΦΑΙΝΟΤΥΠΟΣ ΤΗΣ ΠΝΕΥΜΟΝΙΚΗΣ ΥΠΕΡΤΑΣΗΣ ΣΤΟ ΣΚΛΗΡΟΔΕΡΜΑ

- Myocardial involvement – PH due to left heart disease
- PAH – vasculopathy of pulmonary arteries
- Veno-onclusive PH (fibrosis of pulmonary veins)
- Hypoxia-induced PH due interstitial lung disease

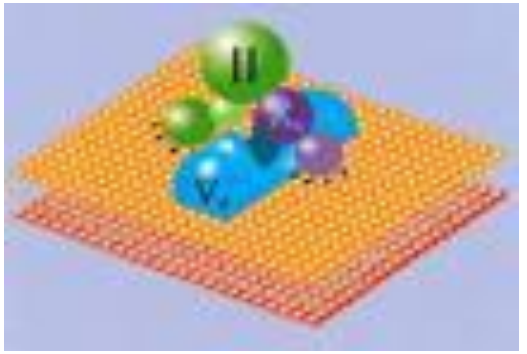


Dimitroulas et al, Nat Rev Rheumatol 2012

ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ ΣΤΟ ΣΕΛ

Άγνωστη συχνότητα (0.5-35%)

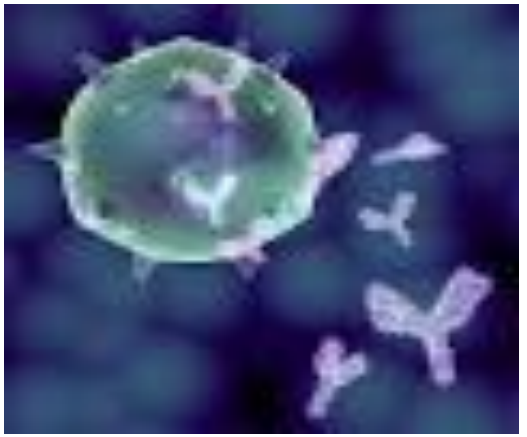
- PAH
- PH λόγω υποξίας



Αντιφωσφολιπικό σύνδρομο
ACL, LAC, β_2 – GPI

✓ Βαλβιδοπάθειες → δευτεροπαθή PH

✓ Θρομβοεμβολικά επεισόδια → Χρόνια θρομβοεμβολική PH

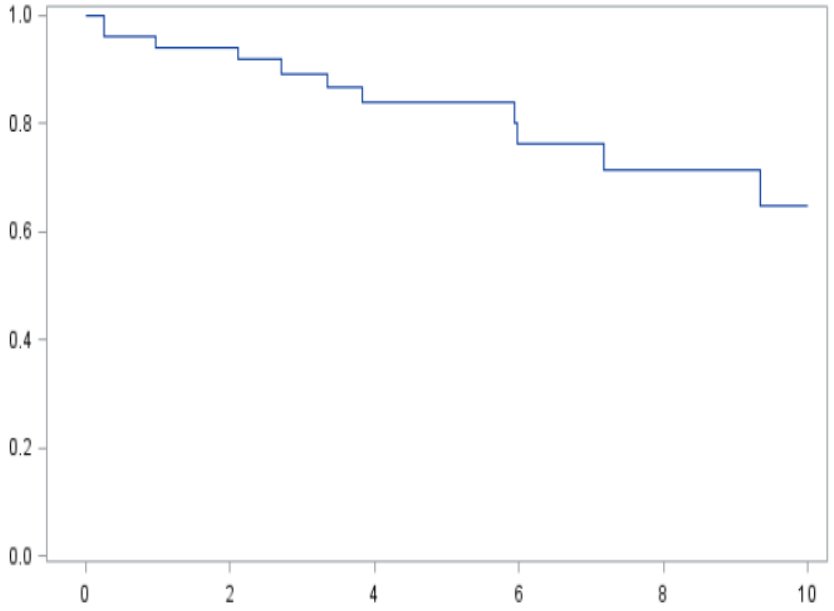


ΜΕΓΑΛΥΤΕΡΗ ΣΥΜΜΕΤΟΧΗ ΤΗΣ ΑΥΤΟΑΝΟΣΙΑΣ ΣΤΗΝ ΑΝΑΔΙΑΜΟΡΦΩΣΗ ΤΟΥ ΠΝΕΥΜΟΝΙΚΟΥ ΑΓΓΕΙΑΚΟΥ ΔΕΝΤΡΟΥ

Chest. 2018 Jan;153(1):143-151. doi: 10.1016/j.chest.2017.08.014. Epub 2017 Aug 26.

Pulmonary Arterial Hypertension Associated With Systemic Lupus Erythematosus: Results From the French Pulmonary Hypertension Registry.

Hachulla E[1], Jais X[2], Cinquetti G[3], Clerson P[4], Rottat L[2], Launay D[5], Cottin V[6], Habib G[7], Prevot G[8], Chabanne C[9], Foïs E[10], Amoura Z[11], Mouthon L[12], Le Guern V[12], Montani D[2], Simonneau G[2], Humbert M[2], Sobanski V[5], Sitbon O[2]; French Collaborators Recruiting Members(*).

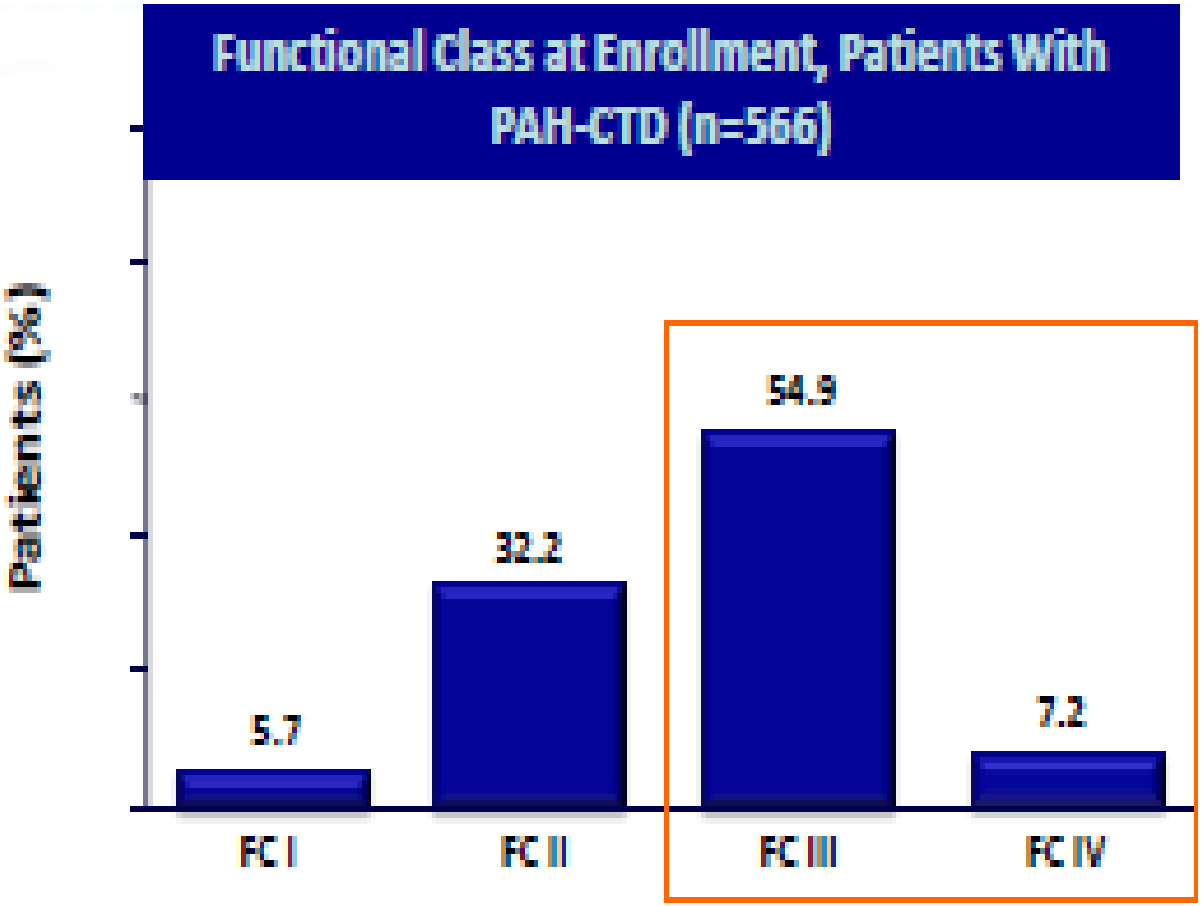


Three and five-year overall survival rates were 89.4% and 83.9%

Years	0	1	2	3	4	5	6	7	8	9	10
N at risk	51	47	44	35	30	27	20	17	14	13	10

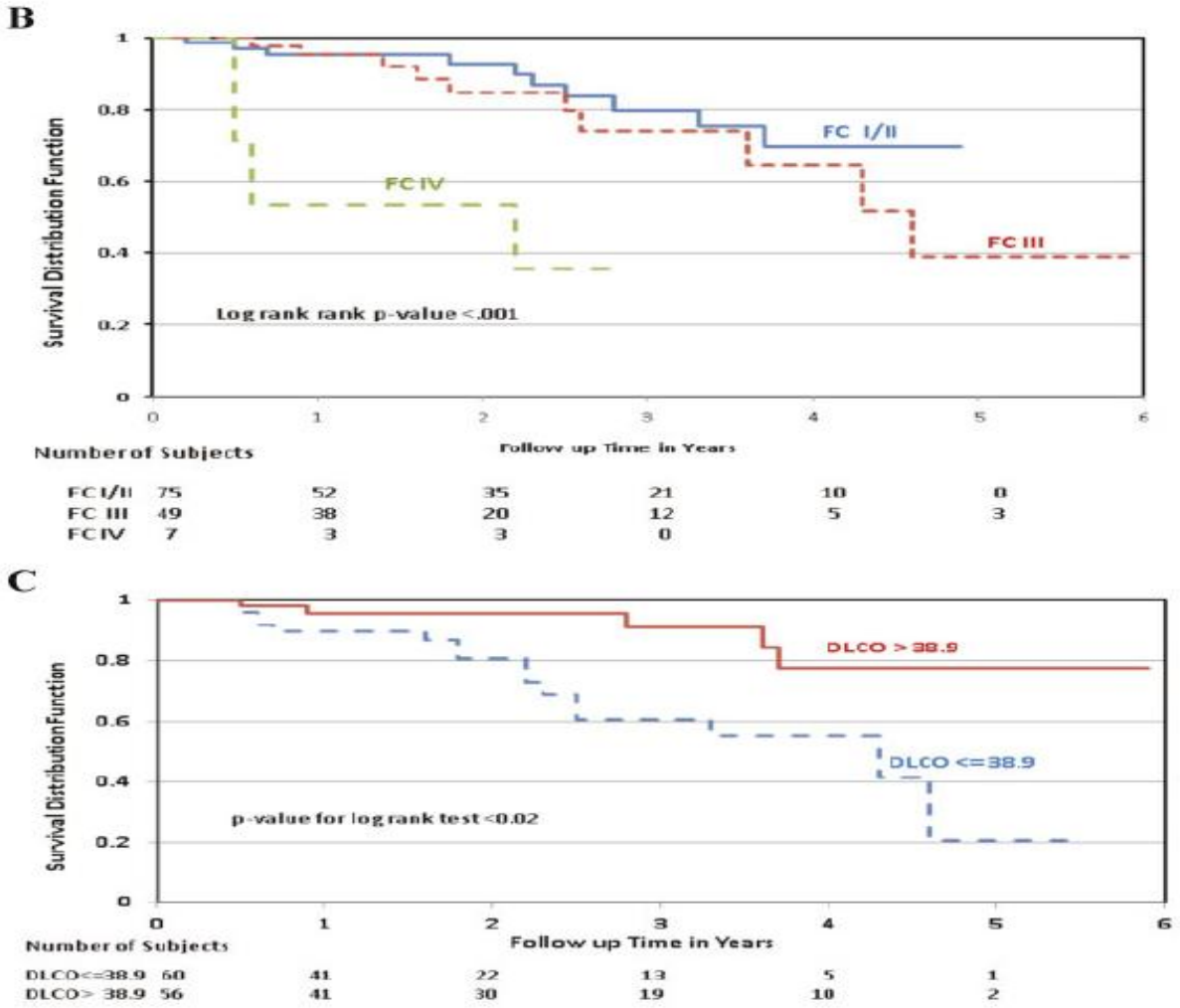
	HR	95% CI	p
Lupus nephritis	12.71	[2.07;60.52]	0.001
Cardiac involvement*	1.92	[0.49;7.46]	0.35
IgG anticardiolipin antibodies	1.48	[0.43;5.01]	0.53
Anti-U1-RNP antibodies**	-	-	0.04
Anti-SSA antibodies	0.34	[0.08;1.44]	0.14
Anti-SSB antibodies***	-	-	0.17
NYHA III-IV	0.80	[0.25;2.93]	0.80
6-min walk distance (by 10 m)	0.97	[0.90;1.05]	0.47
DLCO (% of predicted)	0.98	[0.92;1.03]	0.36
mPAP (mmHg)	1.02	[0.98;1.07]	0.36
PVR (by 80 dyn.sec.cm-5)	1.23	[1.08;1.41]	0.002
Treatment with hydroxychloroquine	0.31	[0.09;1.11]	0.07

ΔΙΑΓΝΩΣΗ ΠΑΥ



Chung et al, Chest 2010

ΠΡΟΓΝΩΣΤΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ

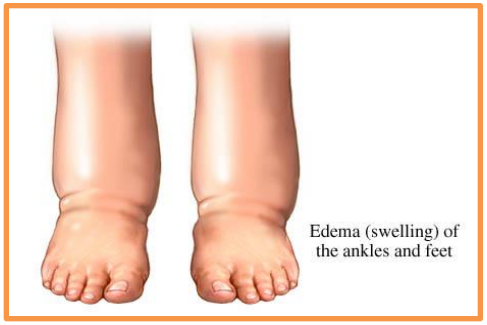


Chung L et al Arthritis Care Res 2013

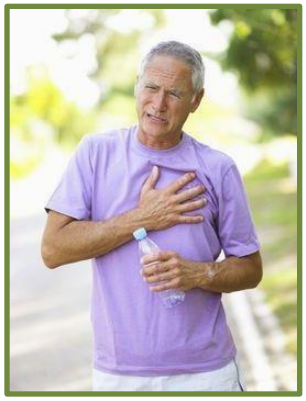
Doc, I am getting short of breath!

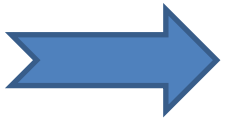
ΚΛΙΝΙΚΗ ΣΥΜΠΤΩΜΑΤΟΛΟΓΙΑ

- ‘Ηπια συμπτώματα



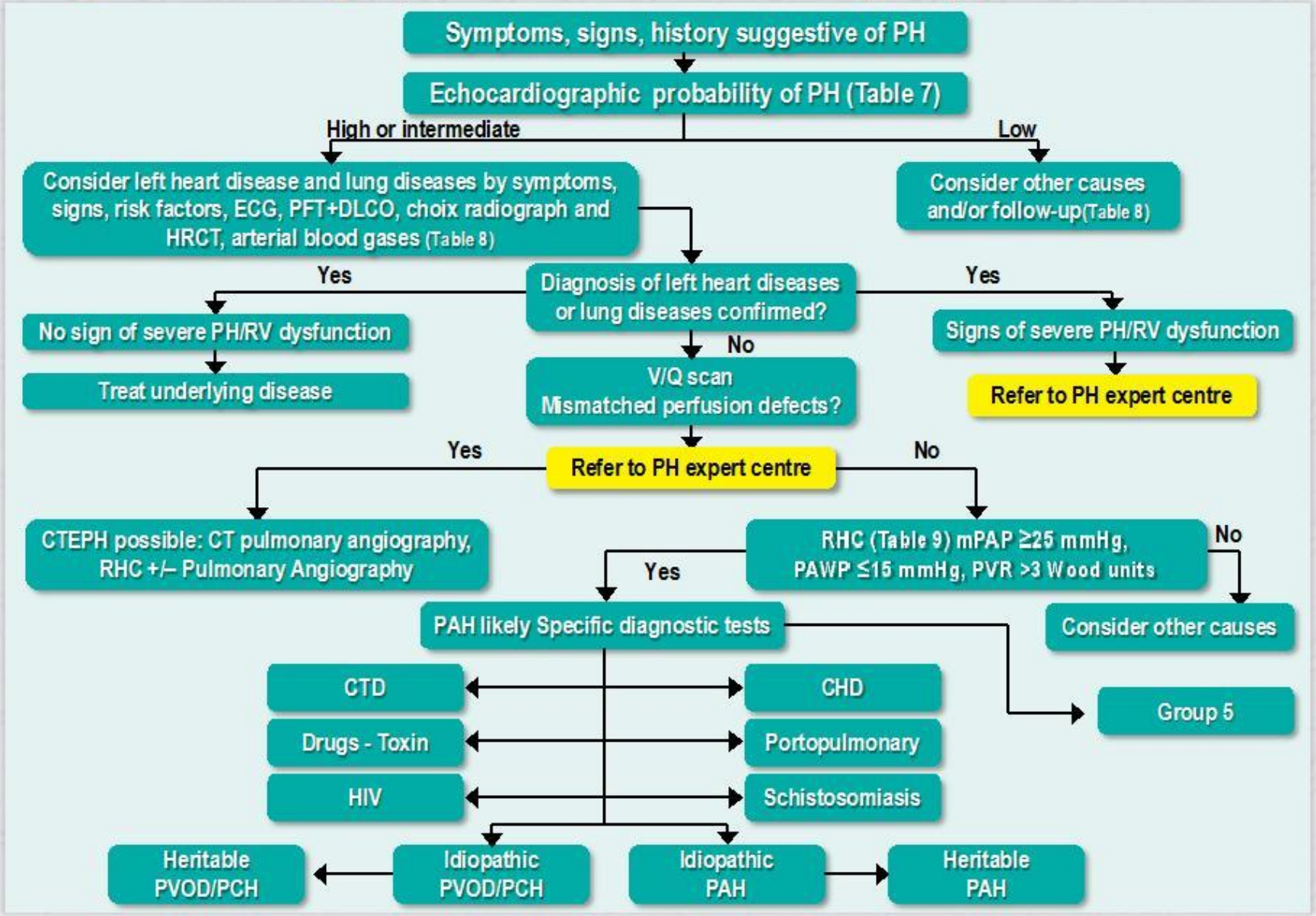
- Μη ειδικά





Delayed diagnosis

Diagnostic Algorithm for Pulmonary Hypertension



European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension according with PTRV & additional signs

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo "PH signs"	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	B: Pulmonary artery	C: Inferior vena cava and right atrium
Right ventricle/ left ventricle basal diameter ratio >1.0.	Right ventricular outlflow Doppler acceleration time <105 m/sec 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..	

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

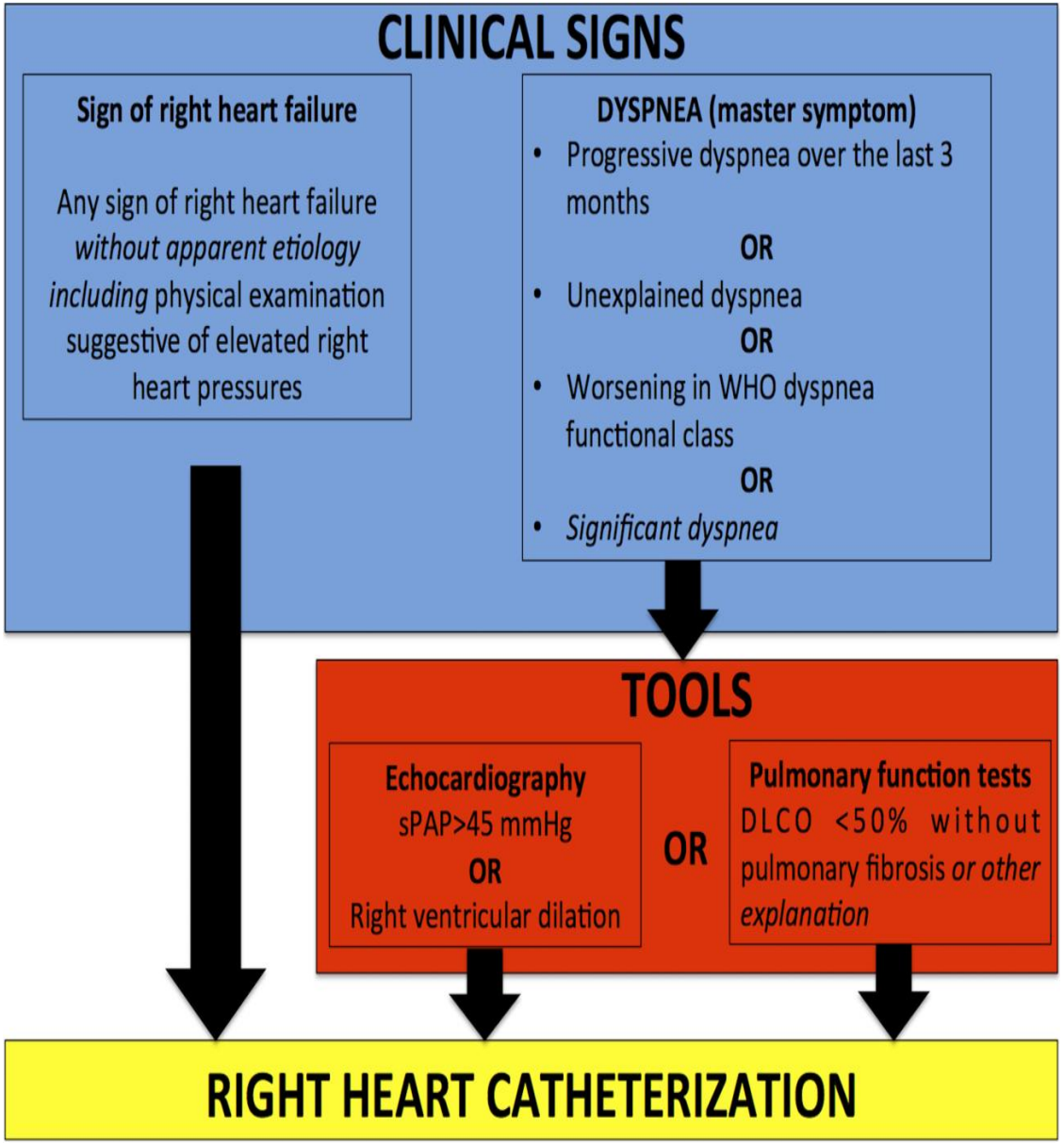
Pulmonary arterial hypertension associated with connective tissue disease

Recommendations	Class	Level
In patients with PAH associated with CTD the same treatment algorithm as for patients with IPAH is recommended.	I	C
Resting echocardiography is recommended as a screening test in asymptomatic SSc patients with systemic sclerosis, followed by annual screening with echocardiography, DLCO and biomarkers.	I	C
RHC is recommended in all cases of suspected PAH associated with CTD.	I	C
Oral anticoagulation may be considered on an individual basis and in the presence of thrombophilic predisposition.	IIb	C

CTD = connective tissue disease.
IPAH = idiopathic pulmonary arterial hypertension.
PAH = pulmonary arterial hypertension.
RHC = right heart catheterization.

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Συμφωνία ειδικών (expert consensus) για τη διενέργεια δεξιού καρδιακού καθετηριασμού σε ασθενείς με σκληρόδερμα.



Avouac et al, Ann Rheum Dis 2013

DETECT

DETECTion of PAH in SSc

Step 1

FVC % pred./DLCO % pred.

Alternatively, enter FVC and DLCO separately

Telangiectasias — yes / no

Anti-centromere antibody (ACA) — pos. / neg.

NTproBNP — pg/ml

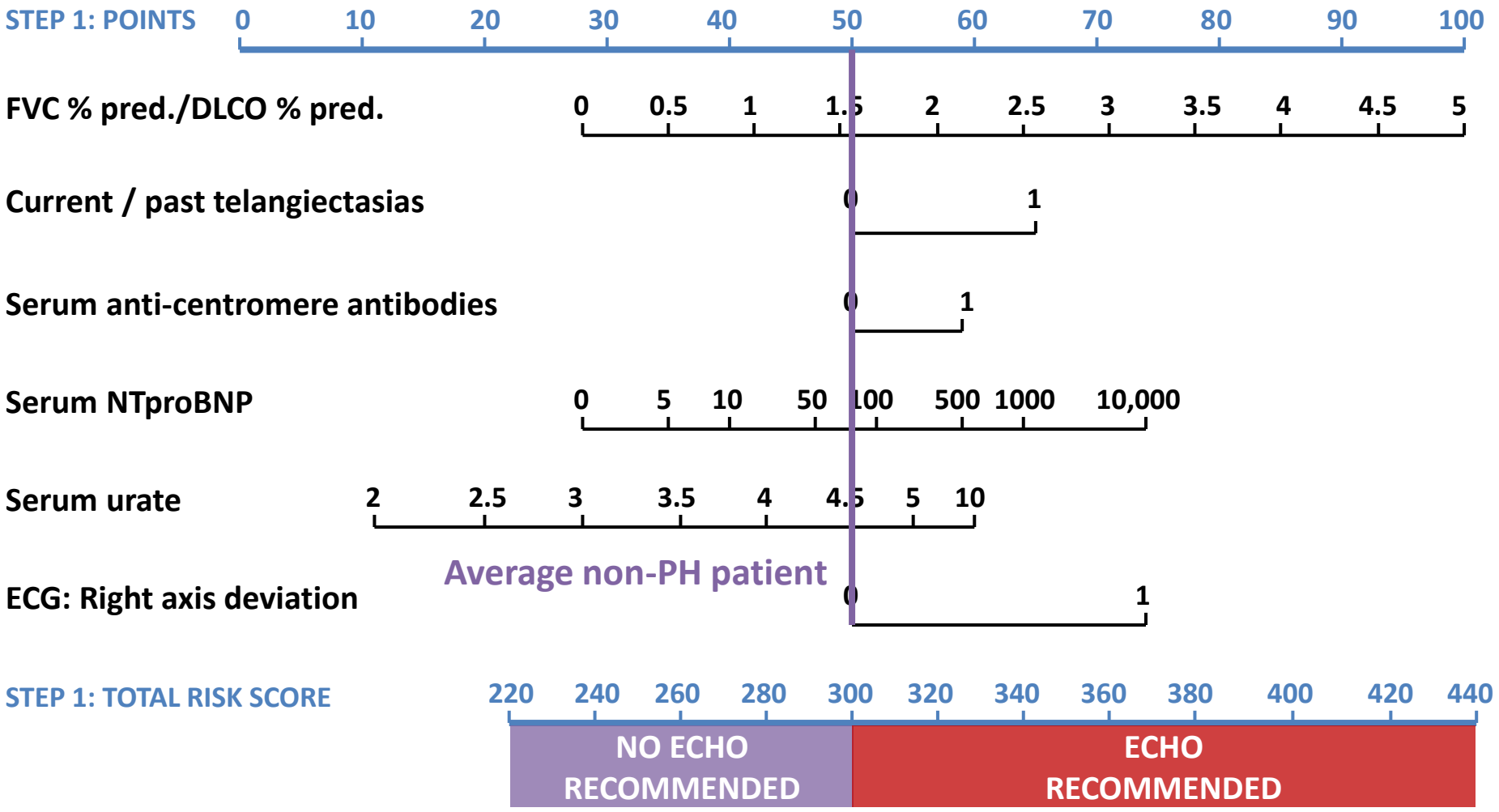
Serum urate — mg/100ml

Right axis deviation on ECG — yes / no

CALCULATE

Step 1 total risk score

DETECT algorithm nomogram step 1: Average non-PH patient



DLCO: Pulmonary diffusing capacity for carbon monoxide;
FVC: forced vital capacity; NTproBNP: N-terminal pro-brain natriuretic peptide.

Recommendations for Screening and Detection of Connective Tissue Disease–Associated Pulmonary Arterial Hypertension

Dinesh Khanna,[1] Heather Gladue,[1] Richard Channick,[2] Lorinda Chung,[3] Oliver Distler,[4] Daniel E. Furst,[5] Eric Hachulla,[6] Marc Humbert,[7] David Langleben,[8] Stephen C. Mathai,[9] Rajeev Saggar,[10] Scott Visovatti,[1] Nezam Altorok,[1] Whitney Townsend,[1] John FitzGerald,[5] and Vallerie V. McLaughlin[1]

ARTHRITIS & RHEUMATISM
Vol. 65, No. 12, December 2013, pp 3194–3201

- Διαθωρακικό ECHO σε ετήσια βάση ανεξάρτητα από την παρουσία συμπτωμάτων
- Διαθωρακικό ECHO με την εμφάνιση ή επιδείνωση δύσπνοιας
- NT-proBNP με την εμφάνιση συμπτωμάτων
- Λειτουργικές δοκιμασίες πνευμόνων + DLCO σε ετήσια βάση
- Λειτουργικές δοκιμασίες πνευμόνων + DLCO σε περίπτωση εμφάνισης ή επιδείνωσης ύποπτων συμπτωμάτων

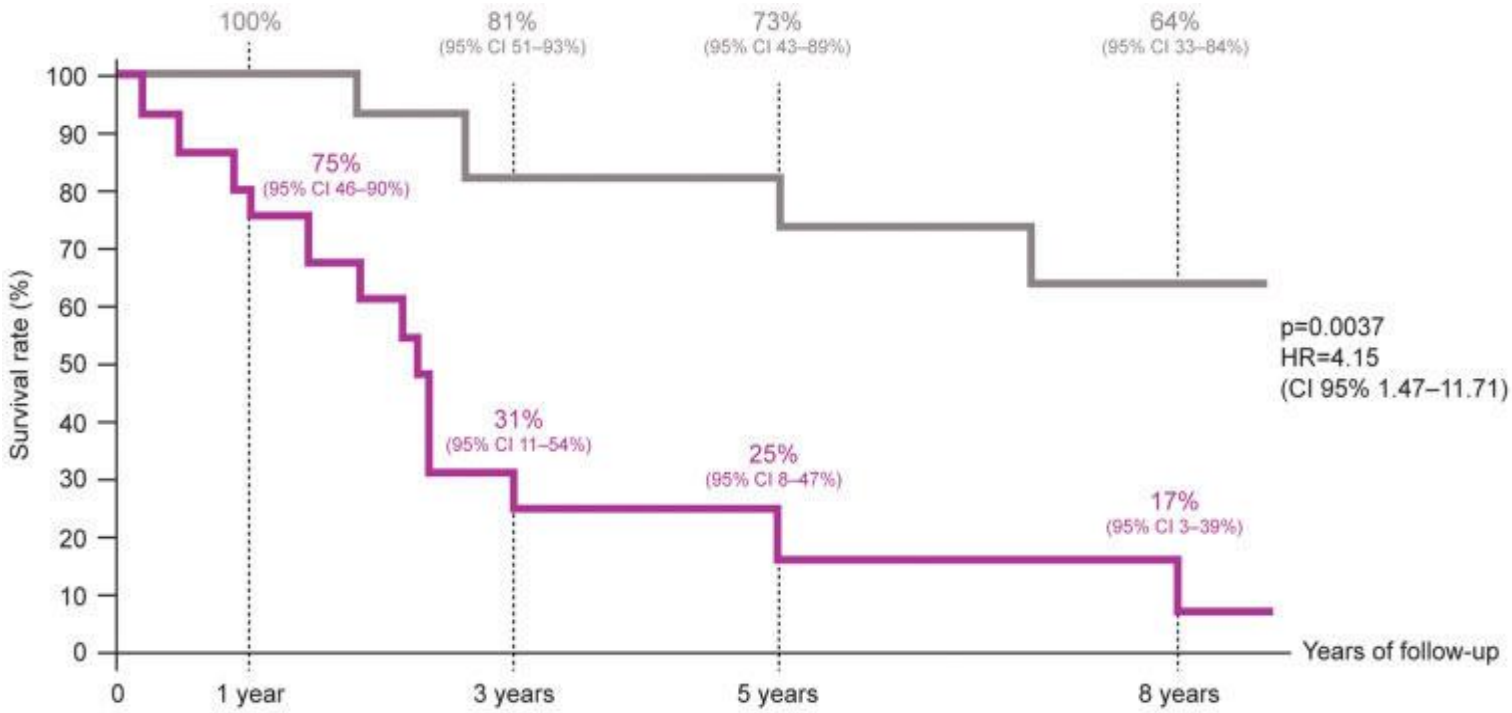
Arthritis & Rheumatology
AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY
Systemic Sclerosis | Free Access

Screening for pulmonary arterial hypertension in patients with systemic sclerosis: Clinical characteristics at diagnosis and long-term survival

Marc Humbert, Azzedine Yaici, Pascal de Groote, David Montani, Olivier Sitbon, David Launay, Virginie Gressin, Loïc Guillevin, Pierre Clerson, Gérald Simonneau, Eric Hachulla

Systemic PAH detection program (n= 16)

Diagnosis during routine clinical practice (n=16)



Humbert et al, Arthritis & Rheum 2011

Arthritis & Rheumatology
AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY
AMERICAN COLLEGE OF RHEUMATOLOGY

Systemic Sclerosis | Free Access

Screening for pulmonary arterial hypertension in patients with systemic sclerosis: Clinical characteristics at diagnosis and long-term survival

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Systemic PAH detection program (n= 16)	Routine Practice (n=16)
Lower mPA (34mmHg)	Higher mPA (49mmHg)
Lower PVRI (613)	Higher PVRI (1500)
Higher CI (3,42L/mlm^2)	Lower CI (2,37L/mlm^2)
NYHA I/II	NYHA III/IV

Humbert M et al Arthritis Rheum 2011

ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ - ΘΕΡΑΠΕΙΑ

Pulmonary arterial hypertension associated with connective tissue disease

Recommendations	Class	Level
In patients with PAH associated with CTD the same treatment algorithm as for patients with IPAH is recommended.	I	C
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CTD = connective tissue disease.
IPAH = idiopathic pulmonary arterial hypertension.
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ERS EUROPEAN RESPIRATORY SOCIETY

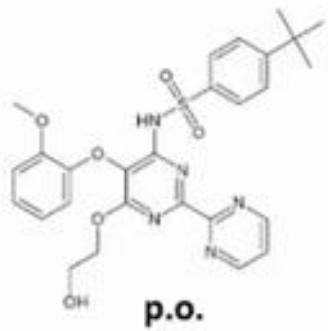
EUROPEAN SOCIETY OF CARDIOLOGY

www.escardio.org

European Heart Journal 2016;37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Licensed targeted therapies for PAH in systemic sclerosis

Endothelin receptor antagonists

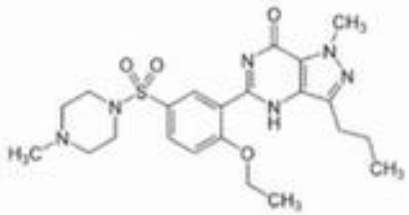


p.o.

Bosentan* (approved 2001)
Ambrisentan
~~Sitaxentan~~ (withdrawn)
Macitentan (approved 2013)

Mechanism ET1 ⇩

Nitric oxide pathway stimulants

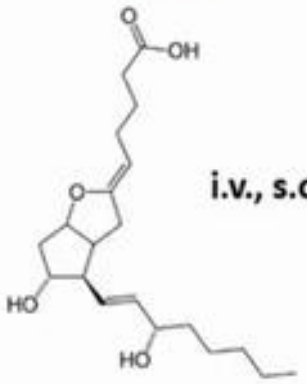


p.o.

Sildenafil (approved 2005)
Tadalafil
Riociguat – guanylate cyclase agonist (approved 2013)

NO
cGMP ⬆

Prostacyclin analogues



i.v., s.c., inh.

Epoprostenol
Treprostinil
Iloprost*
Selexipag (approved 2015)
Beraprost

PGI_2 ⬆

Efficacy of drug monotherapy, for PAH (Group 1)

Recommendations			Class - Level					
Measure/treatment			WHO-FC II		WHO-FC III		WHO-FC IV	
Calcium channel blockers			I	C	I	C	-	-
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C
	Bosentan		I	A	I	A	IIb	C
	Macitentan[d]		I	B	I	B	IIb	C
Phosphodiesterase type-5 inhibitors	Sildenafil		I	A	I	A	IIb	C
	Tadalafil		I	B	I	B	IIb	C
	Vardenafil*		IIb	B	IIb	B	IIb	C
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C
Prostanoids	Epoprostenol	intravenous[d]	-	-	I	A	I	A
	Iloprost	Inhaled	-	-	I	B	IIb	C
		Intravenous*	-	-	IIa	C	IIb	C
	Treprostinil	subcutaneous	-	-	I	B	IIb	C
		Inhaled*	-	-	I	B	IIb	C
		Intravenous[e]	-	-	IIa	C	IIb	C
		Oral*	-	-	IIb	B	-	-
	Beraprost*		-	-	IIb	B	-	-
IP-receptor agonists	Selexipag (oral)*		I	B	I	B		

[c]Only in responders to acute vasoreactivity tests: Class I for idiopathic PAH, heritable PAH and PAH due to drugs;Class IIa for APAH conditions. - [e]Time to clinical worsening as primary end-point in RCTs or drugs with demonstratedreduction in all-cause mortality. - *In patients not tolerating the subcutaneous form.
*This drug is not approved by the EMA at the time of publication of these guidelines.

Efficacy of initial drug combination therapy, for PAH (Group 1)

Recommendations						
Measure/treatment				III	WHO-FC IV	
Ambrisentan + tadalafil[c]			I	B	IIb	C
Other ERA + PDE-5i			IIa	C	IIb	C
Bosentan + sildenafil		-	IIa	C	IIa	C
Bosentan + i	-	-	IIa	C	IIa	C
Other ostinil	-	-	IIb	C	IIb	C
ther ogues	-	-	IIb	C	IIb	C

ilure as primary end-point in RCTs or drugs with demonstrated reduction in all-cause mortality defined).

www.escardio.org

European Heart Journal 2016;37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

itial drug combination therapy, for PAH

ommendations	Class - Level					
treatment	WHO-FC II		WHO-FC III		WHO-FC IV	
entan added to sildenafil	I	B	I	B	IIa	C
iociguat added to bosentan	I	B	I	B	IIa	C
Selexipag added to ERA and/or PDE-5i	I	B	I	B	IIa	C
Sildenafil added to epoprostenol	-	-	I	B	IIa	B
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C
Bosentan added to epoprostenol	-	-	IIb	C	IIb	C
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C
Other double combinations	IIb	C	IIb	C	IIb	C
Other triple combinations	IIb	C	IIb	C	IIb	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

www.escardio.org

European Heart Journal 2016;37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Ανασοκατασταλτική αγωγή στη θεραπεία της ΡΑΗ

Συνδυασμός υψηλών δόσεων κορτικοστεροειδών + κυκλοφωσφαμίδης

Βελτίωση NYHA, 6MWT (ασθενείς με ήπια ΡΑΗ σχετιζόμενη με ΣΕΛ και μικτή νόσο)

Jais et al, Arthritis Rheum 2008

Sanchez at al, Chest 2006

ΚΑΜΙΑ ΒΕΛΤΙΩΣΗ ΣΤΟΥΣ ΑΣΘΕΝΕΙΣ ΜΕ SScPAH

RHEUMATOLOGY

Pulmonary arterial hypertension in systemic lupus erythematosus may benefit by addition of immunosuppression to vasodilator therapy: an observational study

Sirisha Kommireddy[1], Srinivas Bhyravavajhala[2], Kishorebabu Kurimeti[1], Srinivasa Chennareddy[1], Suresh Kanchinadham[1], Irlapati Rajendra Vara Prasad[1] and Liza Rajasekhar[1]

24 SLE patients received CYC for various reasons (nephritis, severe lung ,CNS involvement etc)

TABLE 5 Comparison of baseline clinical and haemodynamic characteristics between responders and non-responders

	Responders ($n = 11$)	Non-responders ($n = 13$)	P-value
Age, mean (S.D.), years	27.18 (9.62)	23.84 (6.42)	0.19
Duration of SLE, median (range), months	60 (1–144)	18 (4–168)	0.11
Duration of PAH in months, median (range)	3 (0–36)	1 (0–12)	0.23
NYHA functional class			
Classes III and IV	9	4	
Classes I and II	1	5	
Asymptomatic	1	4	
Right ventricular systolic pressure, mean (S.D.), mmHg	64.45 (16.90)	52.46 (22.41)	0.38
SLEDAI before immunosuppression, mean (S.D.)	14.43 (7.21)	14.73 (9.87)	0.94

NYHA: New York Heart Association; PAH: pulmonary arterial hypertension.

Am J Respir Crit Care Med. 2015 Nov 1;192(9):1111-7. doi: 10.1164/rccm.201507-1456OC.

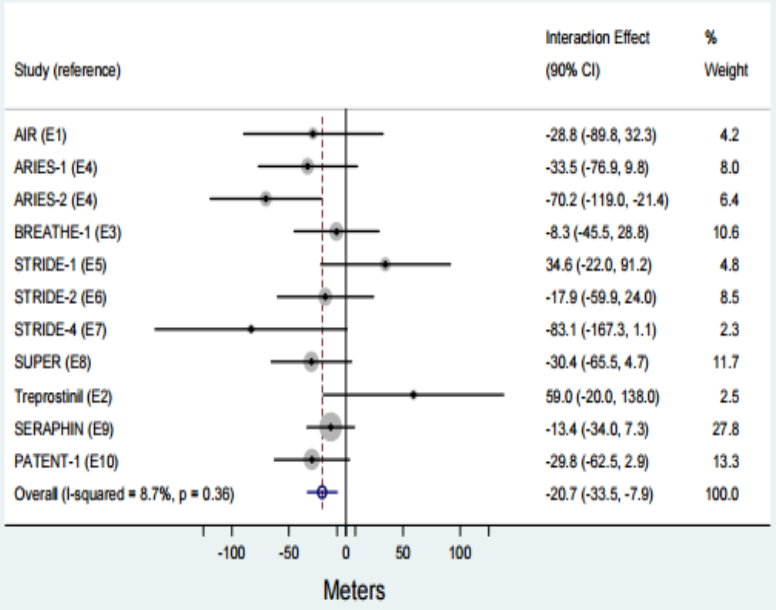
AJRCCM Final Version

Comparison of Treatment Response in Idiopathic and Connective Tissue Disease-associated Pulmonary Arterial Hypertension.

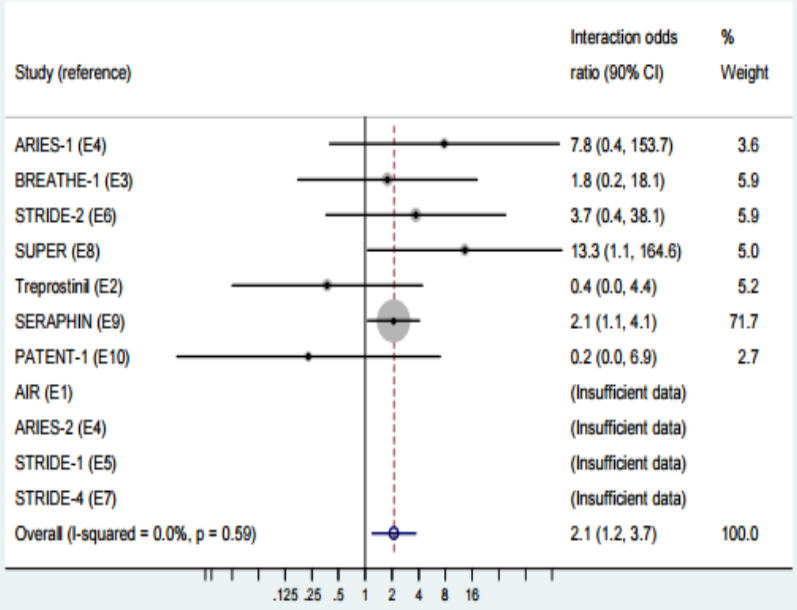
Rhee RL[1], Gabler NB[2], Sangani S[1], Praestgaard A[2], Merkel PA[1,2], Kawut SM[2,3].

IPAH vs SScPAH: τα θεραπευτικά αποτελέσματα στην SScPAH είναι φτωχά

6MWT



CLINICAL WORSENING



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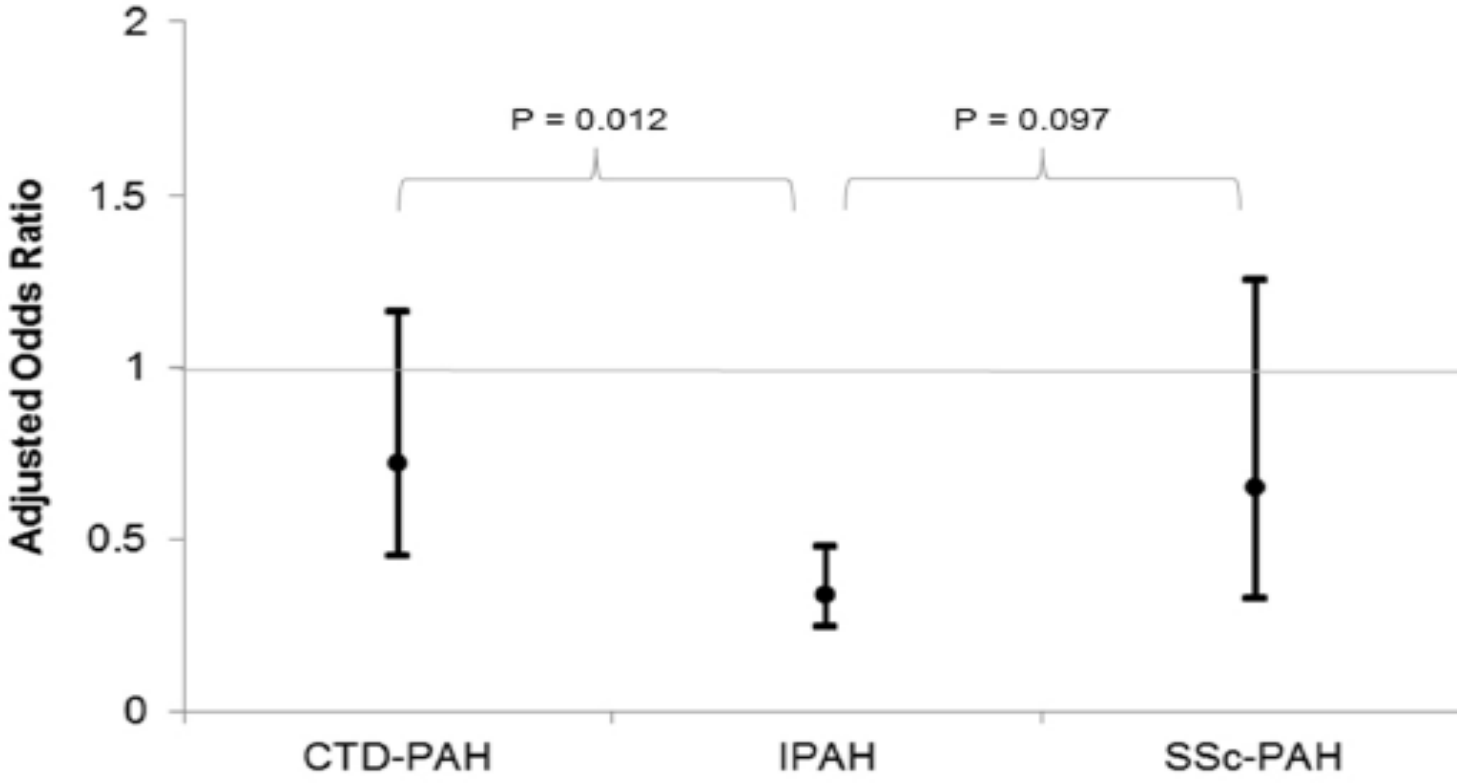
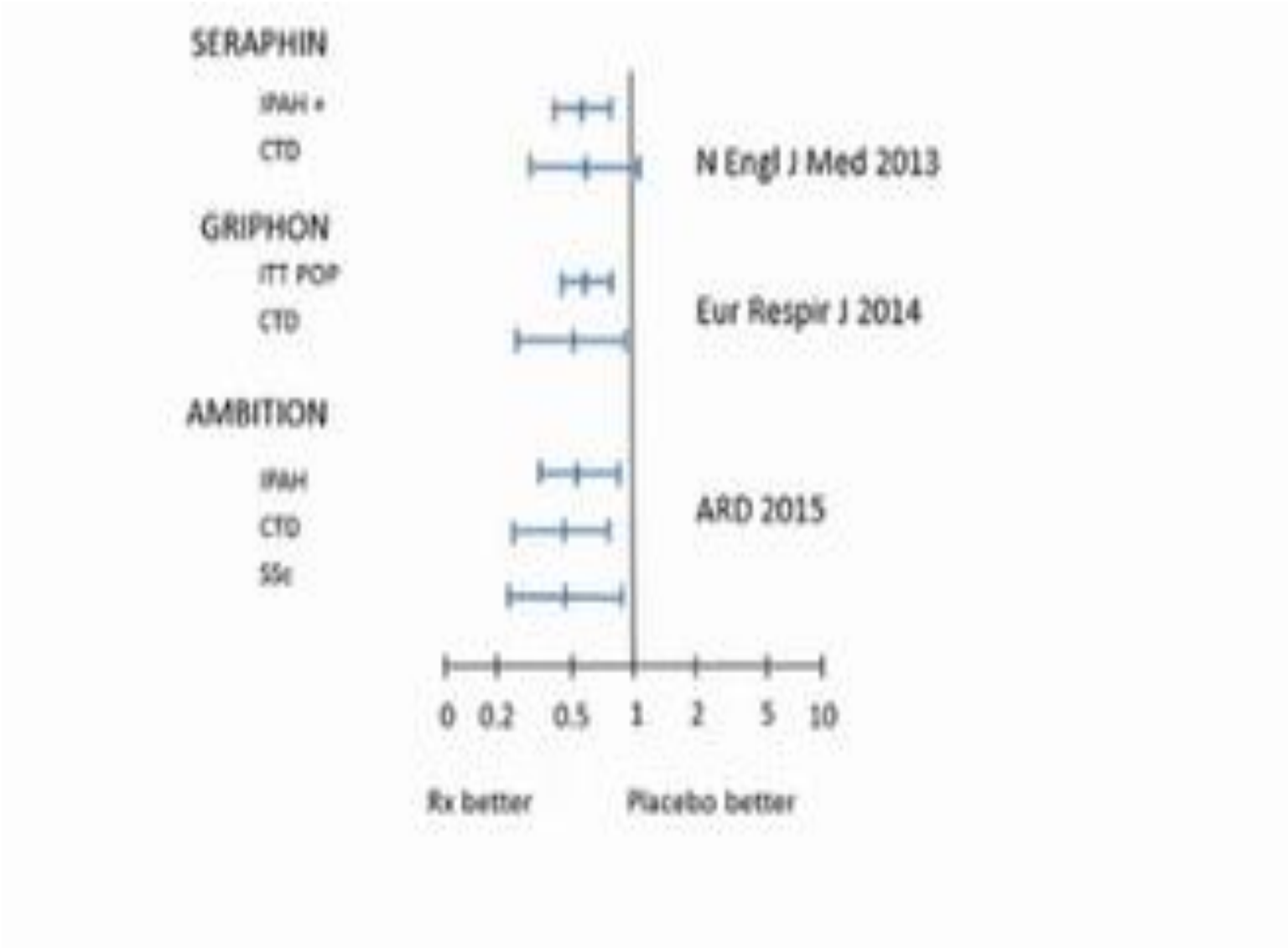


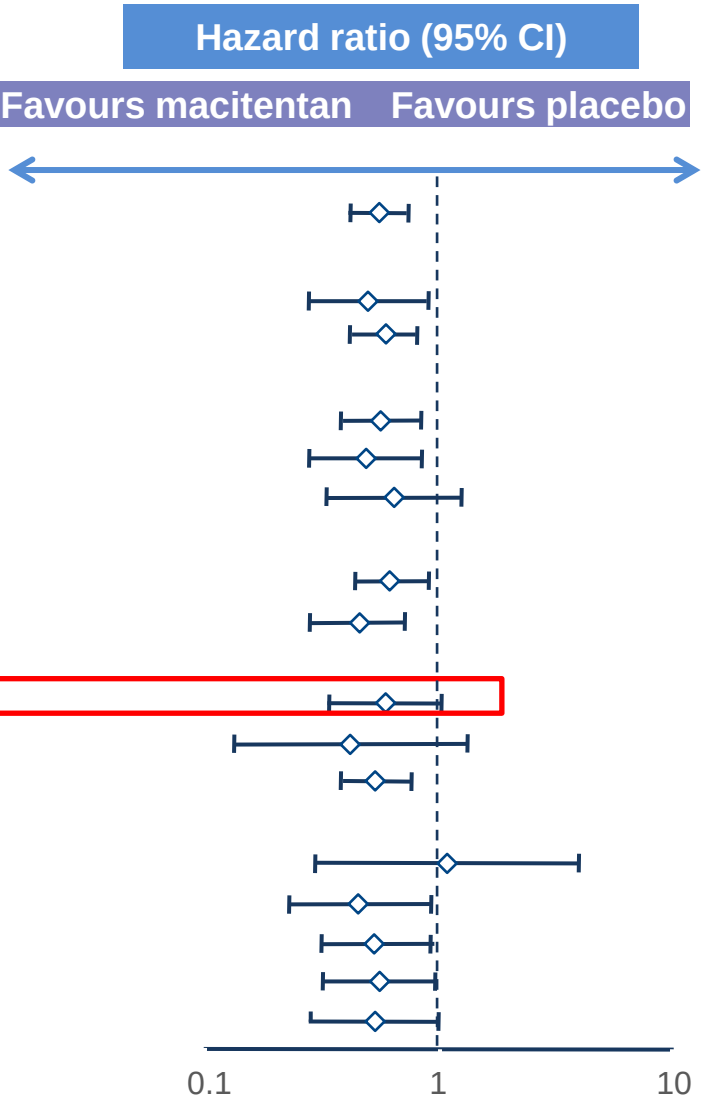
ΝΕΟΤΕΡΕΣ ΘΕΡΑΠΕΙΕΣ ΚΑΙ ΣΣΠΑΥ



MACITENTAN

SERAPHIN STUDY Primary endpoint: Exploratory subgroup analysis

	Macitentan 10 mg	Placebo
All patients	76/242	116/250
Sex (interaction *p* value = 0.73)		
Male	16/48	35/65
Female	60/194	81/185
Race (interaction *p* value = 0.82)		
Caucasian/white	43/135	58/131
Asian	19/65	36/71
Other	14/42	22/48
PAH therapies at baseline (interaction *p* value = 0.24)		
Yes	50/154	68/154
No	26/88	48/96
PAH aetiology (interaction *p* value = 0.84)		
Connective tissue disease	20/73	31/82
Congenital shunts	4/21	10/26
Idiopathic/Other†	52/147	75/140
Geographical region (interaction *p* value = 0.82)		
North America	4/23	5/30
Western Europe/Israel	12/48	21/51
Eastern Europe/Turkey	24/62	33/59
Asia	21/68	33/68
Latin America	15/41	24/42



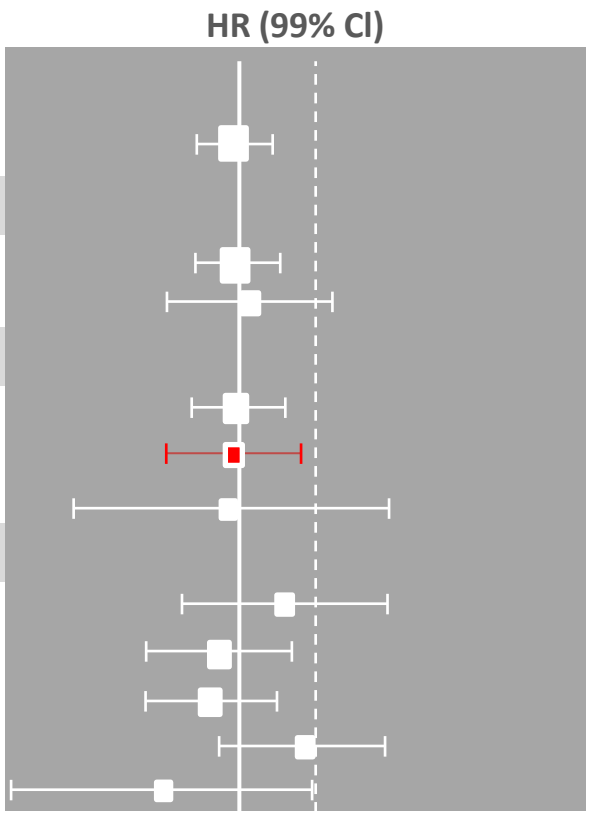
Other aetiology consists of idiopathic or familial PAH, or PAH related to HIV infection or drugs and toxins.

Pulido T, *et al. N Engl J Med* 2013; 369: 809-18.

Selexipag – ΜΕΛΕΤΗ GRIPHON
Consistent treatment effect on the primary composite endpoint across pre-specified subgroups (2)

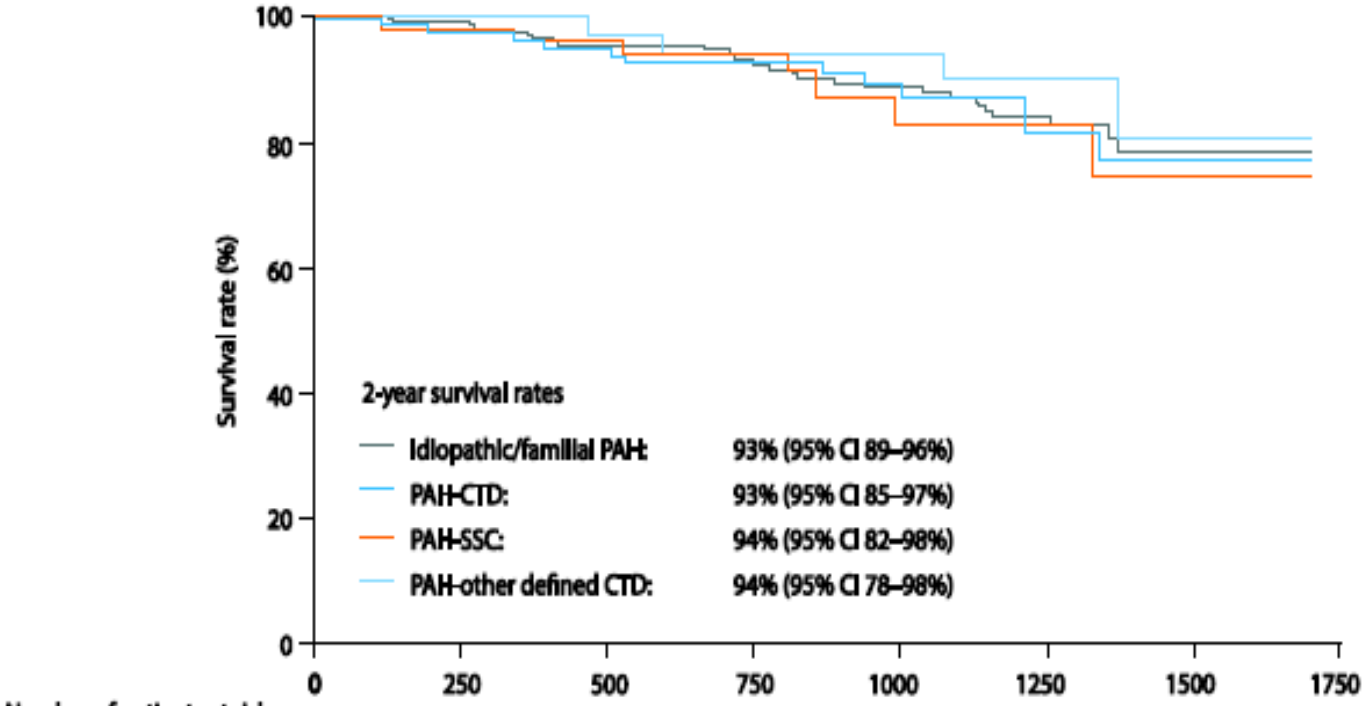
PAH-CTD: 334

Subgroup	*p*-value for interaction	Placebo No. of patients/ no. of events	Selexipag No. of patients/ no. of events
All patients		582/242	574/155
Age at screening	**0.6783**		
< 65 years		474/190	475/124
≥ 65 years		108/52	99/31
PAH aetiology	**0.9765**		
IPAH, HPAH, HIV, drug/toxin-induced		365/156	347/98
PAH-CTD		**167/73**	**167/48**
PAH-CHD		50/13	60/9
Geographical region	**0.0734**		
North America		98/28	95/23
Western Europe/Australia		160/68	161/39
Eastern Europe		155/85	149/48
Asia		113/39	115/37
Latin America		56/22	54/8



Sitbon O, *et al. New Engl J Med* 2015; 373:2522-33

RIOCIGUAT - PATENT -2 STUDY



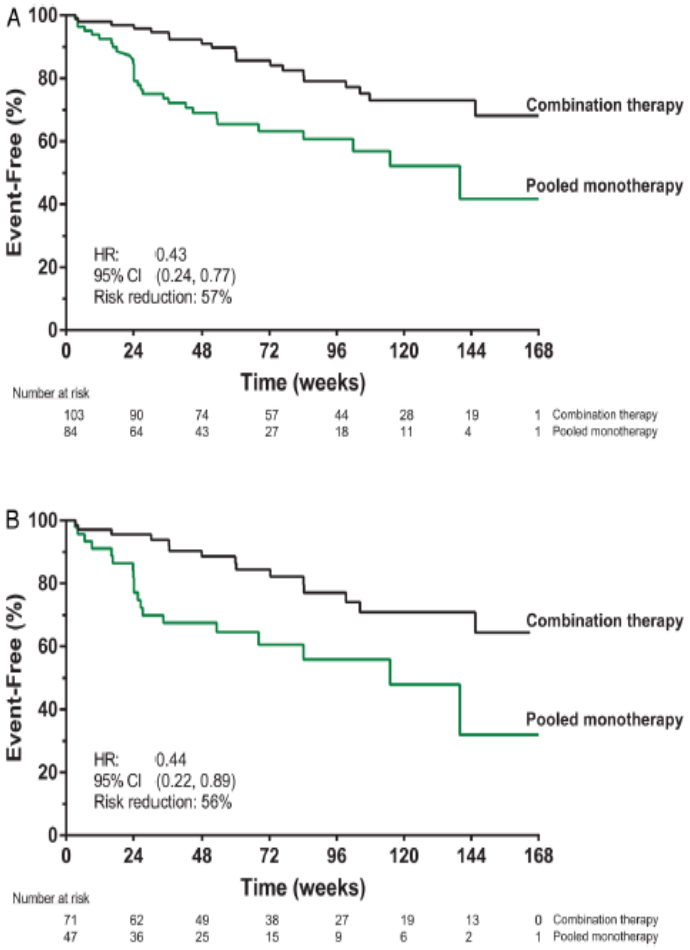
Number of patients at risk

Idiopathic/familial PAH	254	244	225	179	116	69	17
PAH-CTD	94	87	79	63	43	29	6
PAH-SSc	55	49	44	34	20	16	3
PAH-other defined CTD	34	34	31	26	21	13	3

Humbert M et al, Ann Rheum Dis 2017

AMBITION TRIAL (ambrisentan+tadalafil versus monotherapy)

Figure 2 Kaplan-Meier curves for the time from randomisation to first adjudicated clinical failure in the (A) connective tissue disease-associated pulmonary arterial hypertension population and (B) systemic sclerosis-pulmonary arterial hypertension population. Post hoc figures. The HR is for combination versus pooled monotherapy.



Coghlan et al, Ann Rheum Dis 2016

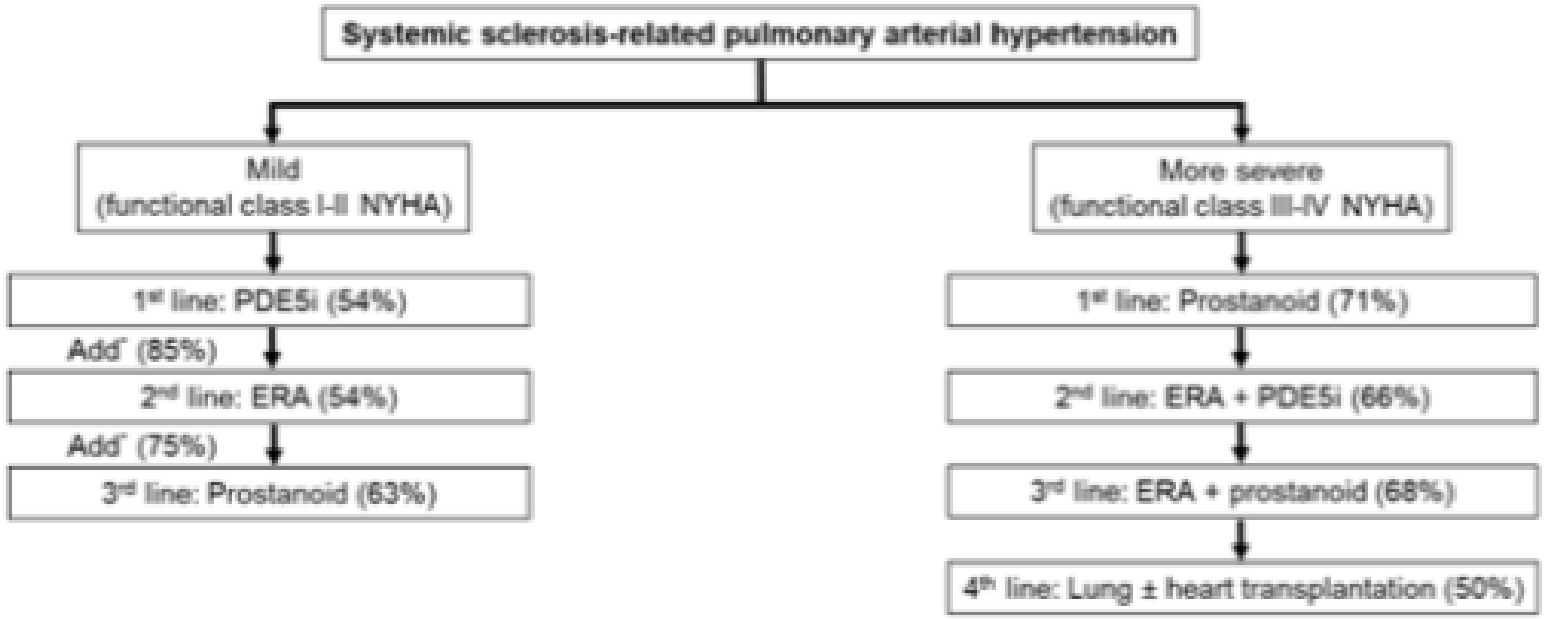
Arthritis & Rheumatology
AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

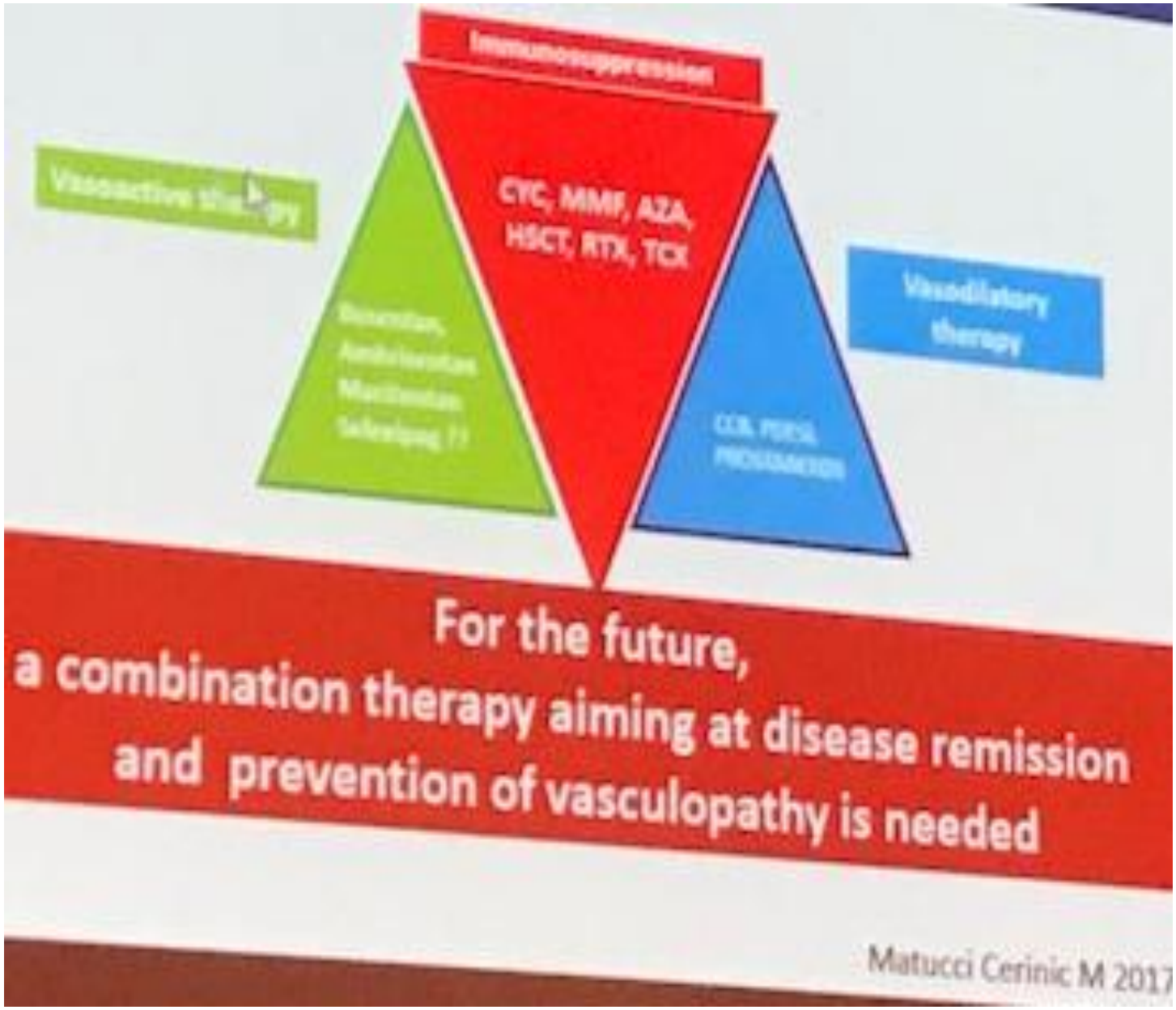
Arthritis Rheumatol. 2018 May 21. doi: 10.1002/art.40560. [Epub ahead of print]

Treatment algorithms for systemic sclerosis according to experts.

Fernández-Codina A[1,2], Walker KM[3], Pope JE[1]; Scleroderma Algorithm Group.

B




Immunosuppression
CYC, MMF, AZA,
HSCT, RTX, TCZ
Vasodilatory
therapy
For the future,
a combination therapy aiming at disease remission
and prevention of vasculopathy is needed
Matucci Cerinic M 2017

Recommendation

Annals of the Rheumatic Diseases

Update of EULAR recommendations for the treatment of systemic sclerosis

Otylia Kowal-Bielecka[1], Jaap Fransen[2], Jerome Avouac[3], Mike Becker[4, 5], Agnieszka Kulak[1], Yannick Allanore[3], Oliver Distler[5], Philip Clements[6], Maurizio Cutolo[7], Laszlo Czirjak[8], Nemanja Damjanov[9], Francesco del Galdo[10], Christopher P Denton[11], Jörg H W Distler[12], Ivan Foeldvari[13], Kim Figelstone[14], Marc Frerix[15], Daniel E Furst[6], Serena Guiducci[16], Nicolas Hunzelmann[17], Dinesh Khanna[18], Marco Matucci-Cerinic[16], Ariane L Herrick[19, 20], Frank van den Hoogen[2], Jacob M van Laar[21], Gabriela Riemekasten[22], Richard Silver[23], Vanessa Smith[24], Alberto Sulli[7], Ingo Tarner[15], Alan Tyndall[25], Joep Welling[26], Frederic Wigley[27], Gabriele Valentini[28], Ulrich A Walker[25], Francesco Zulian[29], Ulf Müller-Ladner[15] EUSTAR Coauthors

Author affiliations +

http://dx.doi.org/10.1136/annrheumdis-2016-209909

Organ involvement	Recommendation 2016	Level of evidence	Stren1Bgth of recommendation
Raynaud	Dihydropiridine – type calcium antagonists IV iloprost – or other available IV prostanoids	1A	A
	PDE-5 inhibitors Fluoxetine	1A 3	A C
Digital ulcers	IV iloprost Bosentan	1B 1B	A A
	PDE-5 inhibitors	1A	A
PAH	ERA PDE-5 inhibitors Riociguat IV epoprostenol	1B 1B 1B 1A	B B B A

ΣΥΜΠΕΡΑΣΜΑΤΑ

- Η ΡΑΗ αποτελεί μία σοβαρή επιπλοκή των ρευματικών νοσημάτων
- Σχετίζεται με διαφορετικούς παθοφυσιολογικούς μηχανισμούς που μπορεί να συνυπάρχουν στον ίδιο ασθενή
- Ο υψηλός βαθμός κλινικής υποψίας και ο συνδυασμός απεικονιστικών και βιοχημικών μεθόδων μπορεί να βοηθήσουν στην έγκαιρη διάγνωση και χορήγηση θεραπείας στα αρχικά στάδια – ΕΓΚΑΙΡΗ ΠΑΡΑΠΟΜΠΗ
- Συνεργασία διαφορετικών ειδικοτήτων για τη διάγνωση και παρακολούθηση της ανταπόκρισης στη θεραπευτική αγωγή που βελτιώνεται με τη συνδυαστική θεραπεία και τις νεώτερες στοχευόμενες θεραπείες.

Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension according with PTRV & additional signs

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo "PH signs"	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	B: Pulmonary artery	C: Inferior vena cava and right atrium
Right ventricle/ left ventricle basal diameter ratio >1.0.	Right ventricular outlflow Doppler acceleration time <105 m/sec 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..	

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Diagnostic management according to echocardiographic probability of PH in patients with symptoms compatible with PH, with or without risk factors for PAH or CTEPH

Echocardiographic probability of PH	Without risk factors or associated condition for PAH or CTEPH[a]	Class	Level
Low	Allternative diagnosis should be considered	IIa	C
Intermediate	Alternative diagnosis, echo follow-up, shoud be considered	IIa	C
	Further investigation of PH may be recommended[b]	IIb	
High	Further investigation of PH (including RHC[b]) is recommended	I	C
Echocardiographic probability of PH	**With risk factors or associated conditions for PAH or CTEPH[a]**	**Class**	**Level**
Low	Echo follow-up should be considered	IIa	C
Intermediate	Further assessment of PH including RHC should be considered[a]	IIa	B
High	Further investigation of PH[b] including RHC is recommended	I	C

CTEPH = chronic thromboembolic pulmonary hypertension; Echo = echocardiographic; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RHC = right heart catheterization.

[a]These recommendations do not apply to patients with diffuse parenchymal lung disease or left heart disease;

[b]Depending on the presence of risk factors for PH group 2, 3 or 5. Further investigation strategy may differ depending on whether risk factors/associated conditions suggest higher probability of PAH or CTEPH – see diagnostic algorithm.

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