



Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης
Α΄ Καρδιολογική Κλινική ΑΧΕΠΑ



Πνευμονική υπέρταση – Απεικόνιση I Υπερηχοκαρδιογραφικοί δείκτες αξιολόγησης κινδύνου

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Ειδ/νη Καρδιολογίας
ΓΠΝ ΑΧΕΠΑ Θεσσαλονίκης



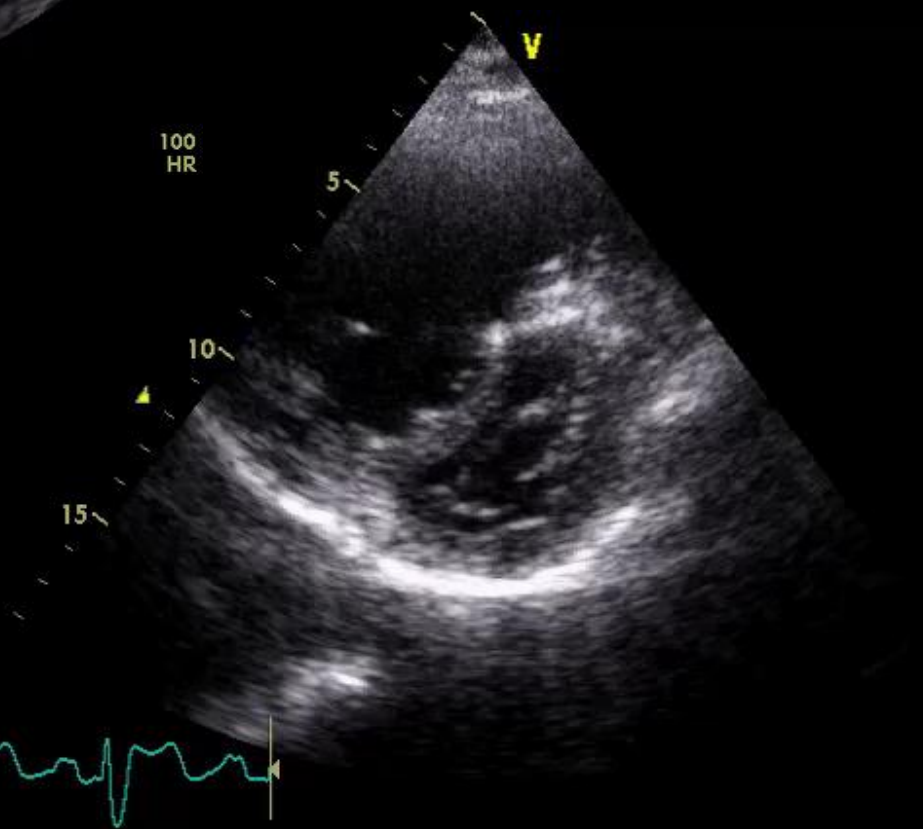


Conflicts of interest: None

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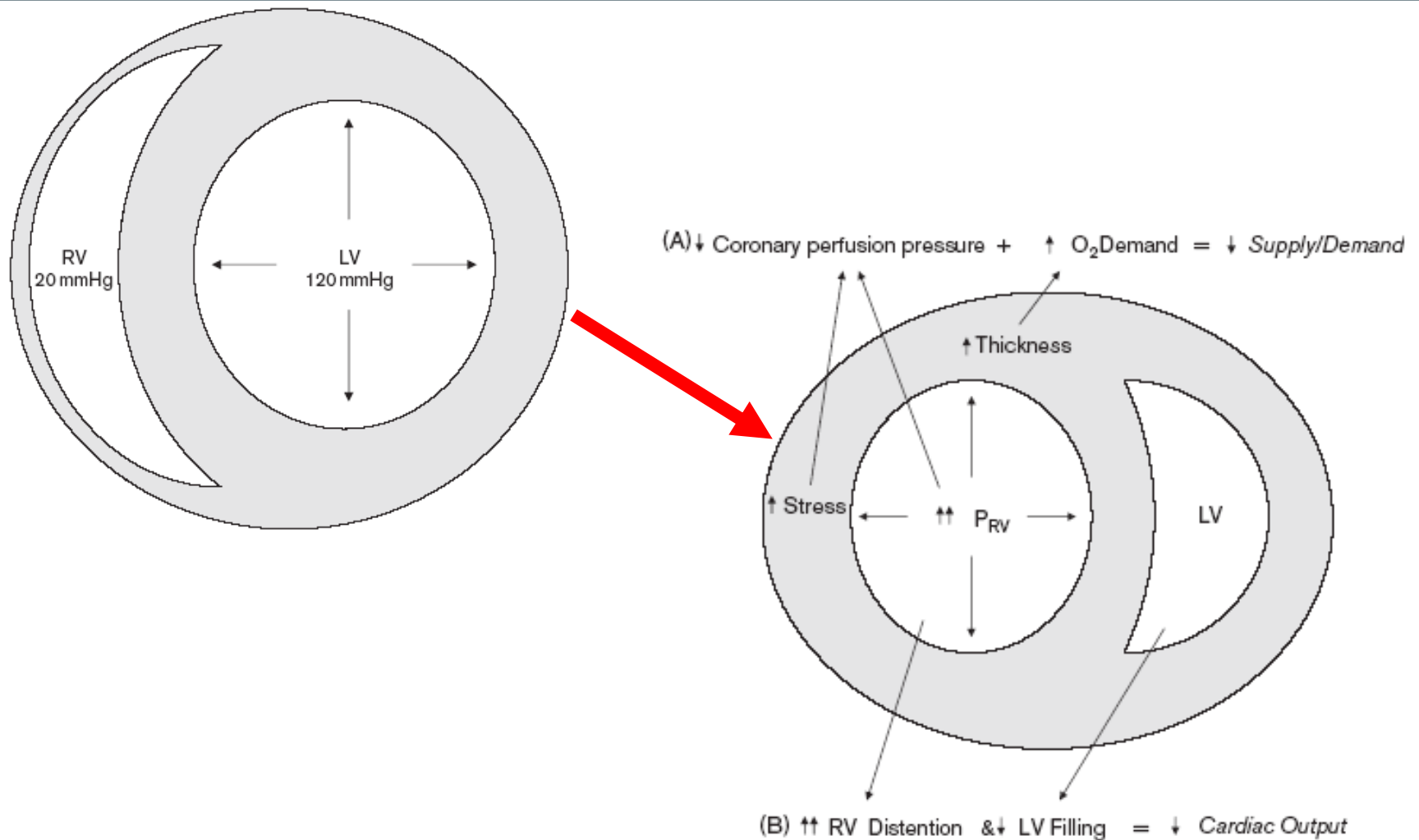


100
HR



97
HR

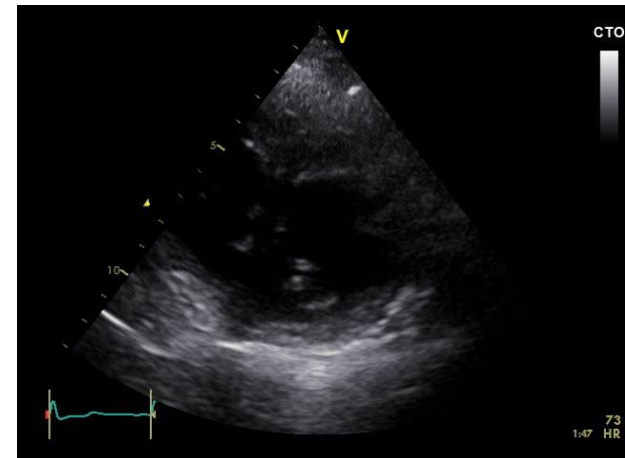
The effect of PH on the RV...



Echocardiography I

Assess:

- cardiac chamber size
- metrics of RV function (TAPSE, FAC)
- myocardial performance indexes
- valvular regurgitation
- valvular function
- pulmonary hemodynamics
- septal curvature
- myocardial deformation imaging





Echocardiography II

- ❑ >50 echo prognostic indexes described in literature
- ❑ The majority examines baseline findings
- ❑ Composite end-points (death, hospitalization, clinical deterioration, treatment uptitration etc)



TABLE 2 Association of PAH Therapy and Echocardiographic RV Parameters

Medication	Specific Drug (Ref. #)	Imaging Tool	Study Design	n	Parameter
Prostacyclins and prostanoids	Parenteral prostacyclin analogues (32)	Echo	1 year follow-up Not placebo controlled	48	Significant improvement in: RVEDA, RVED mid-cavity, TAPSE, RAA, PVR
	Epoprostenol (9)	Echo	12 weeks	81	
	Epoprostenol (43)	Echo	1 year	7	Significant changes in: RA size, diastolic eccentricity index, pericardial effusion score
	Epoprostenol (53)	Echo	Follow-up 5.9 ± 4.6 months	16	Significant change in MPI ($p = 0.05$). RV size and TR severity did not significantly change
Endothelin receptor antagonist	Bosentan	Echo			Significant change in RV size (qualitatively assessed) No significant change in MPI and TR Vmax
	Bosentan BREATH-1 study (19)	Echo	16 weeks of treatment	85 (56 treated)	Change in RV systolic eccentricity ($p = 0.03$) No change in TRV, RVEDA, RV diastolic eccentricity
Combined therapy	Bosentan & prostanoid (54)	Echo	8 ± 3 months Not placebo controlled	37	Significant changes in TAPSE, RV strain, RV strain rate, MPI
	Conventional therapy+ prostacycline (40)	Echo	12 weeks	N = 81, N = 40 on combined therapy	Significantly greater change in RVEDA, systolic and diastolic eccentricity index in combined arm. No comment on combined group changes between baseline and follow-up
	Sildenafil versus bosentan (47)	CMR and echo	16 weeks	25 (13 sildenafil, 12 bosentan)	Significant change in RV mass with sildenafil, not shown with bosentan No significant change in Tei index
	Predominantly ERA (35)	CMR and echo	12 months	91	Significant change in ejection fraction ($p = 0.0001$). No significant change in RVEDVI ($p = 0.22$) or RVmass ($p = 0.68$)

CMR = cardiac magnetic resonance; ERA = endothelin receptor antagonist; MPI = myocardial performance index; PAH = pulmonary artery hypertension; PVR = pulmonary vascular resistance; RAA = right atrial appendage; RV = right ventricular; RVED = right ventricular end-diastolic dimension; RVEDA = right ventricular end-diastolic area; RVEDVI = right ventricular end-diastolic volume index; RVmass = right ventricular mass; TAPSE = tricuspid annular systolic excursion; Tei = total ejection isovolume; TR = tricuspid regurgitation; TRV = tricuspid regurgitation velocity; VTI = velocity time integral.

Λειτουργικότητα δεξιάς κοιλίας	Ογκομετρικές και ανατομικές μετρήσεις
• TAPSE • Επιμήκης μέγιστη συστολική παραμόρφωση της δεξιάς κοιλίας • Κλασματική μεταβολή της επιφάνειας της δεξιάς κοιλίας • Tei index • Χρόνος εξώθησης της δεξιάς κοιλίας • Διάρκεια της ανεπάρκειας της τριγλώχινας βαλβίδας • Λόγος κύματος S:D • Χρόνος ισοογκοτικής χάλασης • Χρόνος ισοογκοτικής επιτάχυνσης • Ρυθμός παραμόρφωσης του ελεύθερου τοιχώματος της δεξιάς κοιλίας • Χρόνος μέχρι τη μέγιστη συστολική παραμόρφωση του ελεύθερου τοιχώματος της δεξιάς κοιλίας • Ρυθμός πρώιμης διαστολικής παραμόρφωσης του ελεύθερου τοιχώματος της δεξιάς κοιλίας • Κυκλοτερής παραμόρφωση της δεξιάς κοιλίας • Ακτινική παραμόρφωση της δεξιάς κοιλίας • Παραμόρφωση της επιφάνειας της δεξιάς κοιλίας	• Επιφάνεια του δεξιού κόλπου • Λόγος επιφάνειας του δεξιού προς τον αριστερό κόλπο • Δείκτης εκκεντρότητας της αριστερής κοιλίας • Ανώμαλη διαμόρφωση του μεσοκοιλιακού διαφράγματος κατά τη τελοδιαστολή • Επιφάνεια της δεξιάς κοιλίας στη τελοδιαστολή και τη τελοσυστολή • Διάμετρος της δεξιάς κοιλίας κατά τη τελοδιαστολή • Λόγος διαμέτρου της δεξιάς προς την αριστερή κοιλία κατά τη τελοδιαστολή • Διάμετρος της δεξιάς κοιλίας στη μεσότητα αυτής • Επιμήκης διάμετρος της δεξιάς κοιλίας • Πάχος του ελεύθερου τοιχώματος της δεξιάς κοιλίας • Τελοδιαστολικός όγκος της αριστερής κοιλίας • Διάμετρος της αριστερής κοιλίας κατά τη τελοσυστολή και τη τελοδιαστολή • VTI_{RVOT}
Λειτουργικότητα αριστερής κοιλίας	Παράμετροι μέτρησης της πίεσης
• Καρδιακή παροχή και καρδιακός δείκτης της αριστερής κοιλίας • Κλάσμα εξώθησης της αριστερής κοιλίας • Επιμήκης μέγιστη συστολική παραμόρφωση της αριστερής κοιλίας • Κυκλοτερής παραμόρφωση της αριστερής κοιλίας • Δυσλειτουργία της αριστερής κοιλίας	• Συστολική πίεση της δεξιάς κοιλίας • Συστολική πίεση στην πνευμονική αρτηρία • Μέγιστη ταχύτητα παλίνδρομης ροής στην τριγλώχινα βαλβίδα • Βαρύτητα της ανεπάρκειας της τριγλώχινας βαλβίδας • Πίεση του δεξιού κόλπου • Χρόνος επιτάχυνσης ροής στην πνευμονική αρτηρία • Χρόνος επιτάχυνσης ροής στον χώρο εξόδου της δεξιάς κοιλίας



Echocardiography III

□ Basic echo predictors

- Right heart enlargement
- RV remodeling – hypertrophy and decreased function
- IVS leftward deviation
- Pericardial effusion



RV

Forward failure

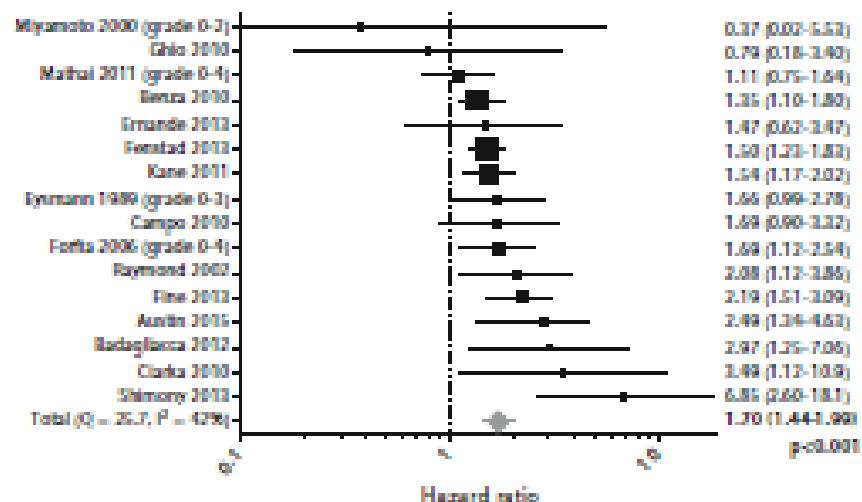
- ❑ Parameters of RV systolic function

Backward failure

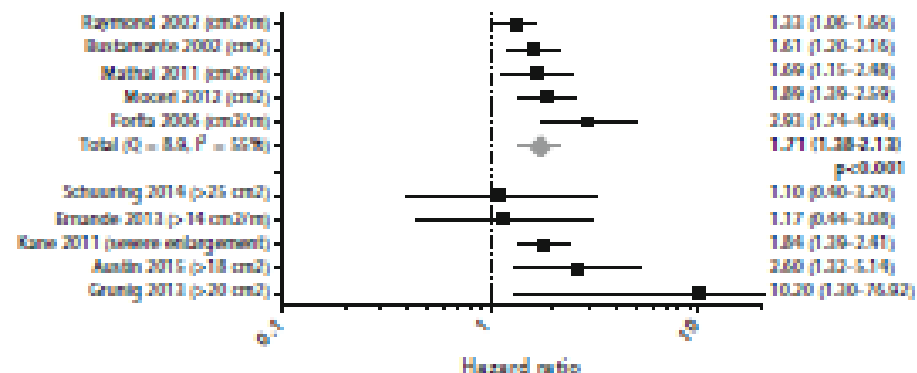
- ❑ Parameters of RV diastolic dysfunction

- ❑ Parameters of R-L asynchrony

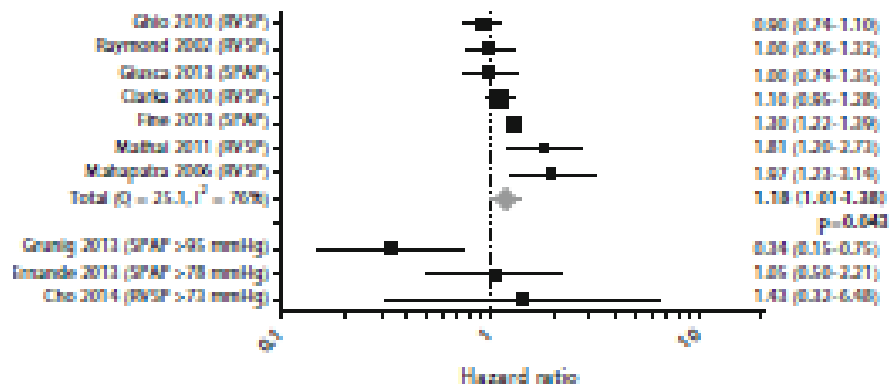
Presence of pericardial effusion



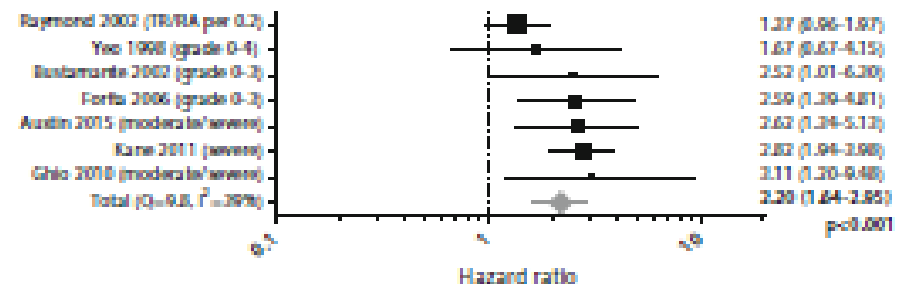
Right atrial area (per 5 cm² increase)



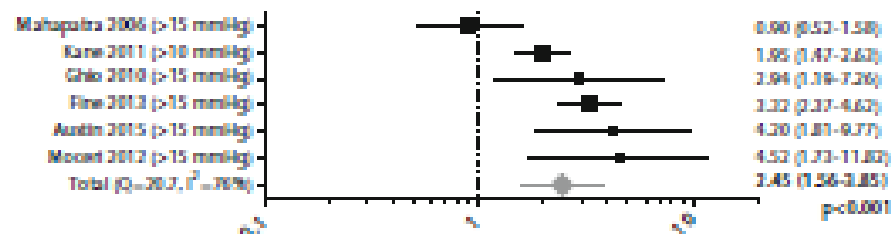
RV pressure estimates (per 10 mmHg increase)



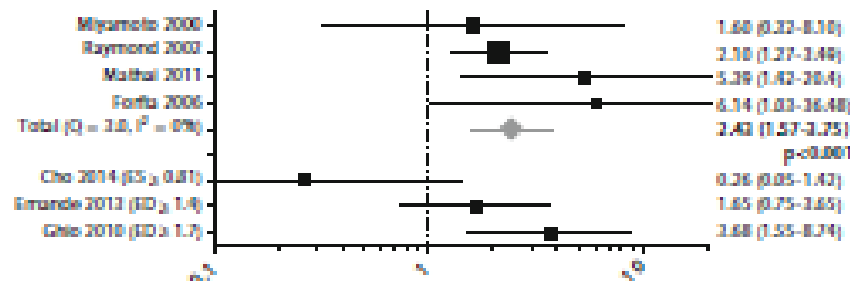
TR severity



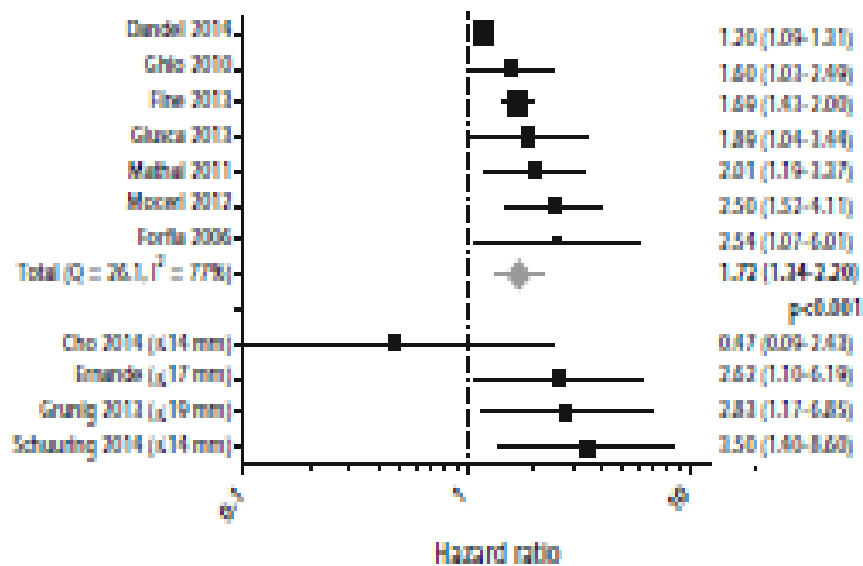
Estimated RA pressure



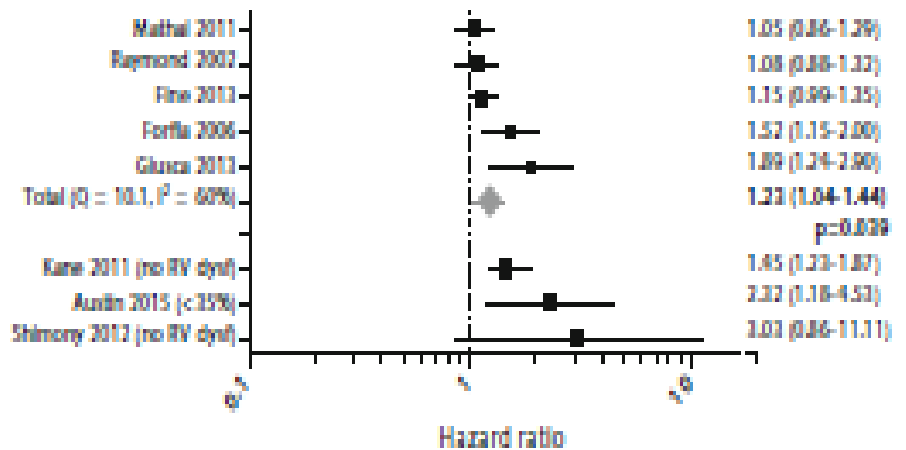
LV eccentricity index



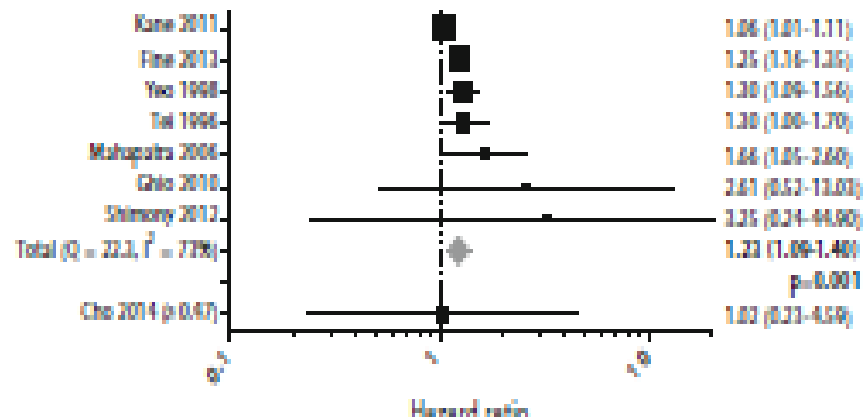
TAPSE (per 5 mm decrease)



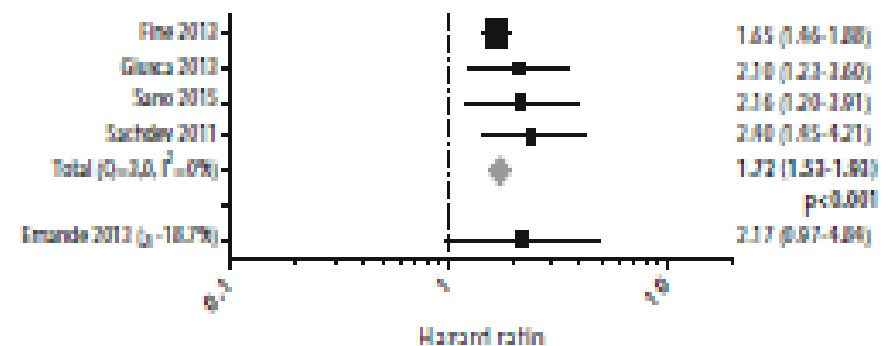
RV fractional area change (per 5% decrease)



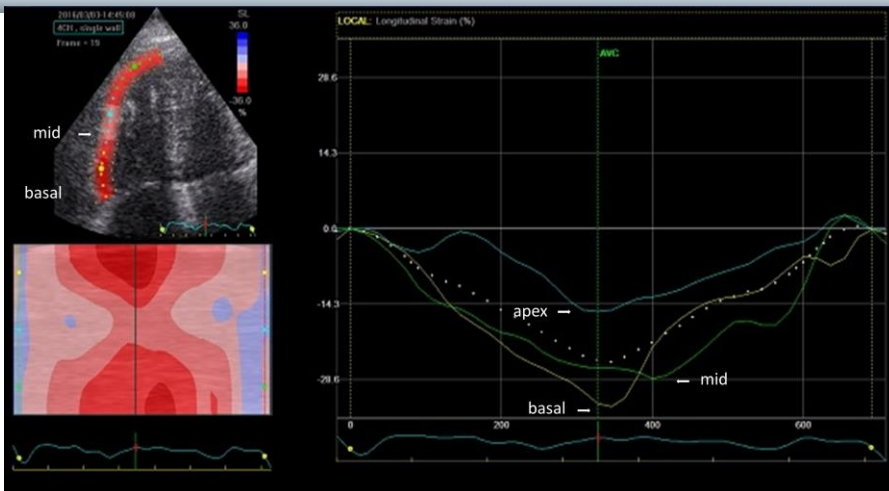
Tai Index (per 0.1 increase)



RV free wall longitudinal peak systolic strain (per 5% decrease)



Echocardiography – modern technologies I



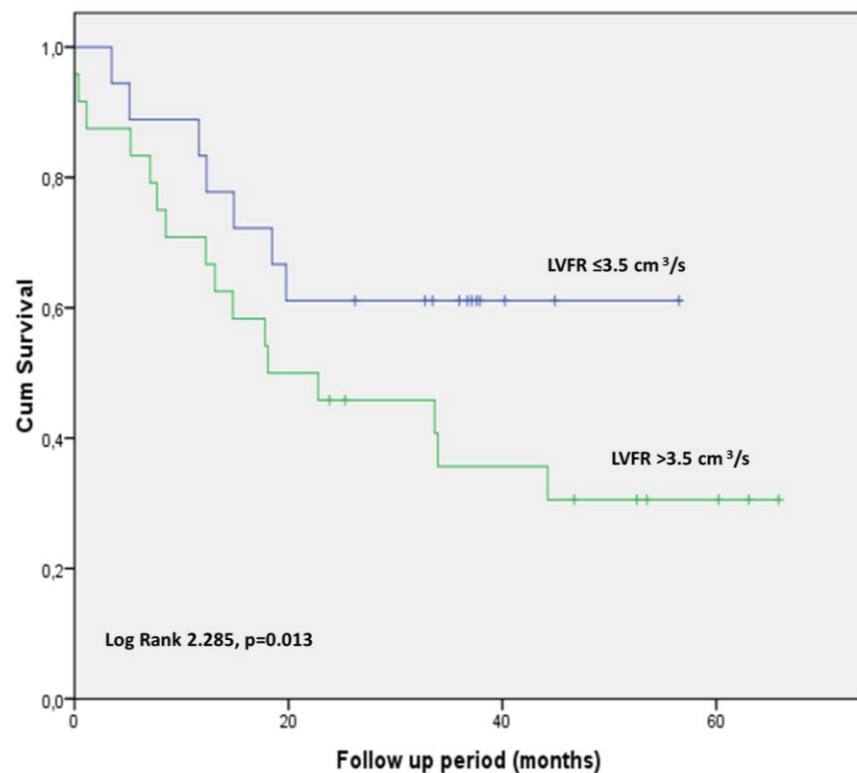
- ❑ In PAH RV strain (area, longitudinal, radial and circumferential) is
 - Reduced
 - Predictive of functional capacity
 - Predictive of survival
- ❑ Serial assessment of RV free wall systolic strain predicts
 - Clinical deterioration
 - Mortality
- ❑ Serial assessment of RV longitudinal strain improves the prediction of long-term outcomes for PH patients over standard hemodynamic indices.

	Multivariable analysis			Model comparison			
	HR	95% CI	P value	-2 LL	χ^2	p-value	c-statistic
Model A (6MWD)	3.769	1.204-11.795	0.023	56.381	16.997	<0.0001	0.712
Model A + RV-LPSS				54.288	17.762	<0.0001	0.796
6MWD	2.928	1.001-9.226	0.011				
RV-LPSS	5.391	1.467-19.814	0.014				
Model B (NT-proBNP)	5.817	1.297-26.100	0.021	65.901	5.420	0.02	0.704
Model B + RV-LPSS				61.808	8.525	0.014	0.760
NT-proBNP	1.001	1.001-1.003	0.043				
RV-LPSS	1.133	1.004-1.279	0.042				
Model C (WHO class)	10.01	2.931-34.190	<0.0001	62.862	6.961	0.008	0.705
Model C + RV-LPSS				60.153	9.662	0.008	0.780
WHO class	4.193	1.119-15.721	0.033				
RV-LPSS	1.102	1.002-1.235	0.045				

Smith BC et al, Am J Coll Cardiol 2014
 Rajagopal S et al, J Am Soc Echocardiogr 2014
 Hardegree EL, Am J Cardiol 2013
 Sano H et al, Can J Cardiol 2015
 Okumura K et al, J Am Soc Echocardiogr 2014
 Mouratoglou SA et al, ESC Annual Congress 2016



LV in PAH prognosis

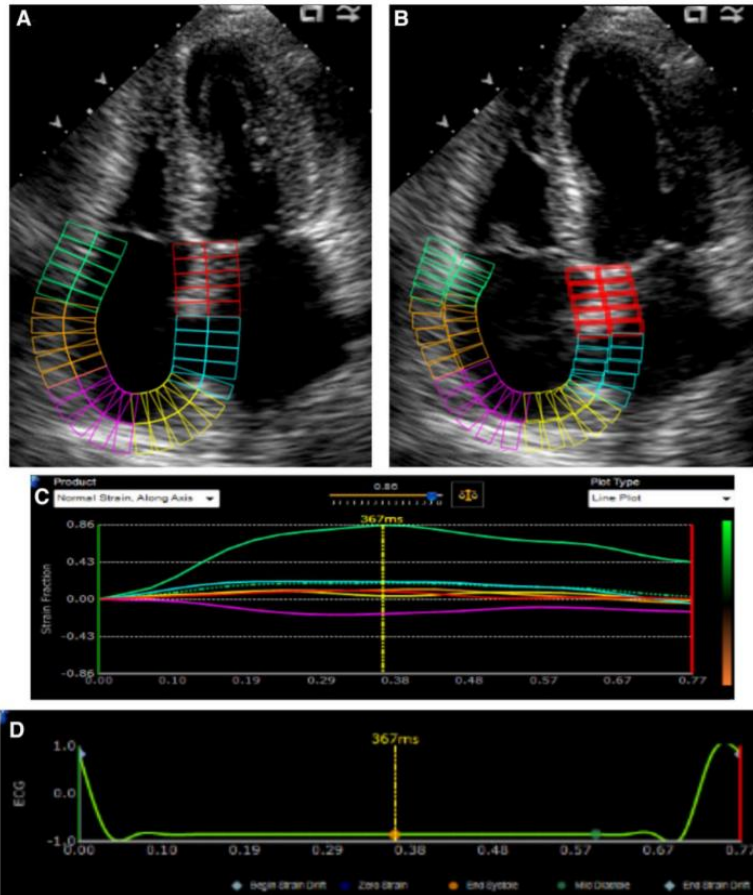


$$\text{LVFR} = \text{E wave} \times 3.14 \times (\text{MAd}/2)^2$$

	Multivariable analysis			Model comparison			
	HR	95% CI	P value	-2 LL	χ ²	p-value	c-statistic
Model A (6MWD)	0.995	0.992-0.998	<0.0001	43.8	8.3	0.004	0.835
Model A + LVFR							
6MWD	0.987	0.977-0.996	0.007	33.37	5.978	<0.0001	0.876
LVFR	1.044	1.040-1.091					
Model B (NT-proBNP)	1.002	1.001-1.004	0.008	41.0	6.961	<0.0001	0.836
Model B + LVFR							
NT-proBNP	1.002	1.001-1.004	0.011	32.9	6.060	<0.0001	0.868
LVFR	1.034	1.010-1.076					
Model C (WHO class)	22.086	2.641-180.726	<0.004	41.0	16.801	<0.0001	0.791
Model C + LVFR							
WHO class	17.256	2.013-147.947	0.006	33.7	17.347	<0.0001	0.847
LVFR	1.033	1.030-1.080					

Table 4. Additive prognostic value of left ventricular filling rate in patients with precapillary pulmonary hypertension
 NT-proBNP: N-terminal pro B-natriuretic peptide, 6MWD: distance walked in six minute walk test, WHO: world health organization, LVFR: left ventricular filling rate

Echocardiography – modern technologies II



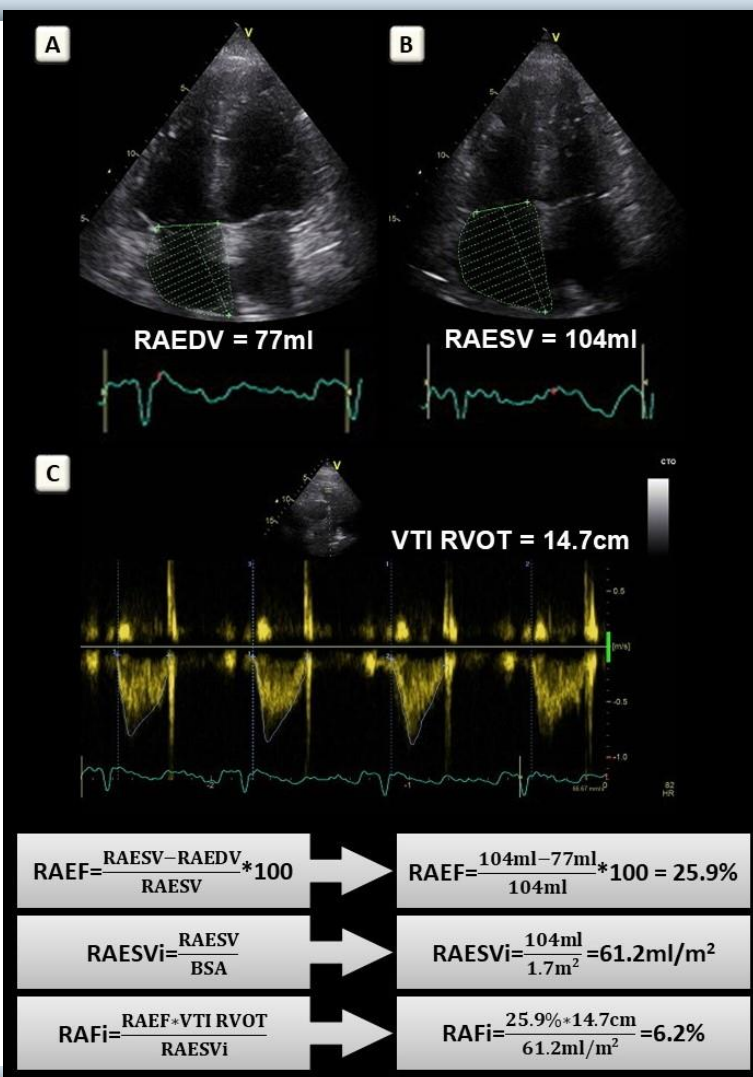
- ❑ Peak RA strain represents the reservoir function of the right atrium
- ❑ In PAH, RA strain
 - Is lower compared to normal controls
 - Is predictive of invasive hemodynamic parameters in group I PAH
 - Predicts clinical outcomes

The role of RA

Would an index incorporating analogues of RA and RV function be of prognostic significance



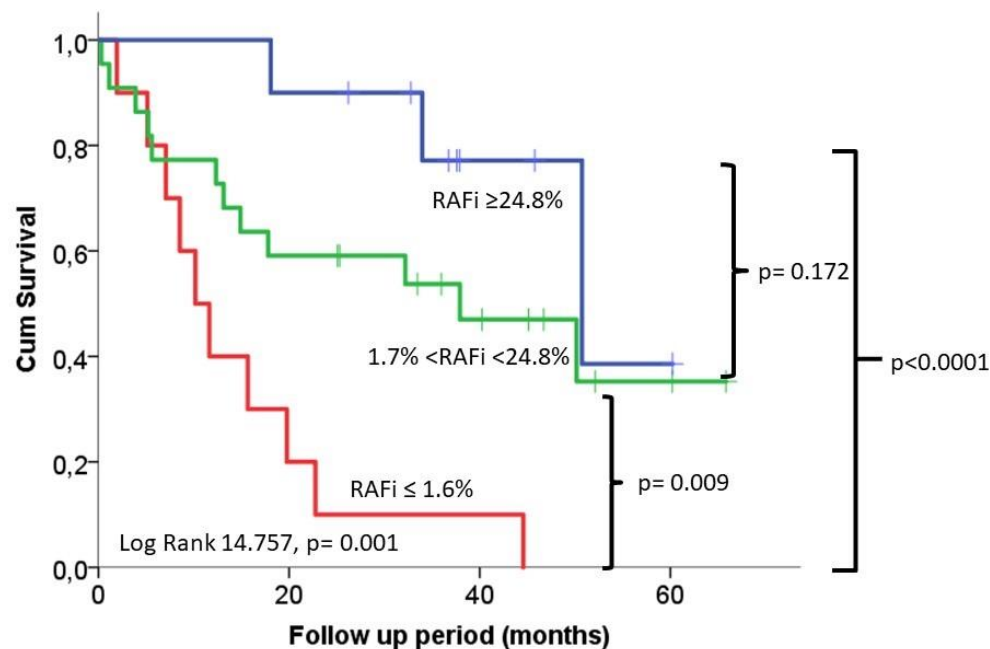
Right atrial function index



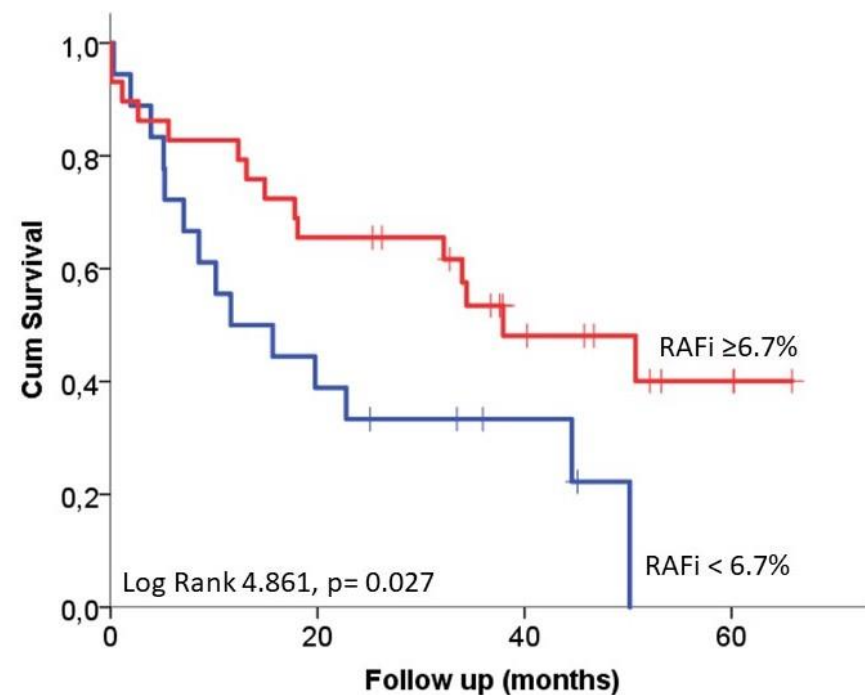
Additive value of RAFi over known survival predictors

Parameter	HR	c-statistic	p-value
6MWD	0.994	0.822	
6MWD+ RAFi	0.952	0.844	<0.0001
NT-pro BNP	1.000	0.737	
NT-pro BNP + RAFi	0.964	0.814	<0.0001
RA area	1.104	0.764	
RA area + RAFi	1.099	0.845	<0.001

HR: hazard ratio, †p-value by Likelihood ratio test of the models without versus with RAFi for each tested parameter



	Month 0	Month 10	Month 20	Month 30	Month 40	Month 50
$RAfi \leq 1.6\%$	15	6	2	1	1	0
$1.7\% < RAfi < 24.8\%$	22	17	13	12	11	10
$RAfi \geq 24.8\%$	10	10	9	8	8	8



	Month 0	Month 10	Month 20	Month 30	Month 40	Month 50
$RAfi < 6.7\%$	18	11	7	5	3	0
$RAfi \geq 6.7\%$	29	24	22	20	19	18



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WHERE DO WE STAND NOW?



The REVEAL risk assessment calculator

PAH
Prognosis

PAH RISK SCORE CALCULATOR¹

For more information go to
www.pah-app.com

Patient: _____ Date: _____

WHO Group I Subgroup	APAH-CTD +1	APAH-PoPH +2	FPAH +2	
Demographics & Comorbidities	Renal insufficiency +1	Male age >60 yrs +2		
NYHA/WHO Functional Class	I -2	III +1	IV +2	
Vital Signs	SBP <110 mm Hg +1	HR >92 BPM +1		
6-Minute Walk Test	≥440 m -1	<165 m +1		
BNP	<50 pg/mL -2	>180 pg/mL +1		
Echocardiogram				
Pericardial effusion +1				
Right-heart Catheterization	mRAP >20 mm Hg within 1 yr +1	PVR >32 Wood units +2		

APAH=associated PAH; BNP=brain natriuretic peptide; BPM=beats per minute; CTD=connective tissue disease; DLco=carbon monoxide diffusing capacity; FPAH=familial PAH; HR=heart rate; mRAP=mean right atrial pressure; NYHA=New York Heart Association; PAH=pulmonary arterial hypertension; PoPH=portopulmonary hypertension; PVR=pulmonary vascular resistance; SBP=systolic blood pressure; WHO=World Health Organization.

SUM OF ABOVE
(Starting Score)

+ 6

= RISK SCORE

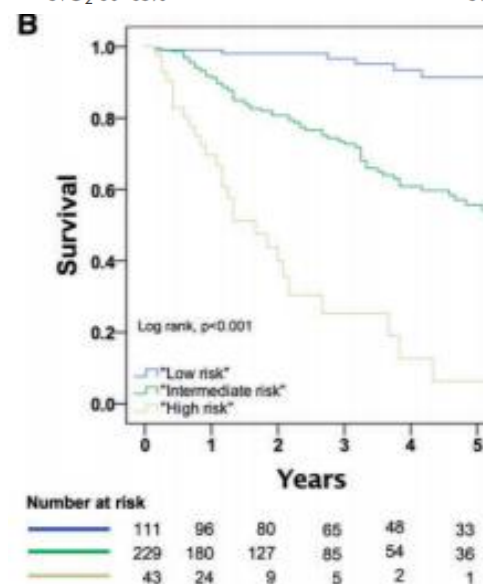
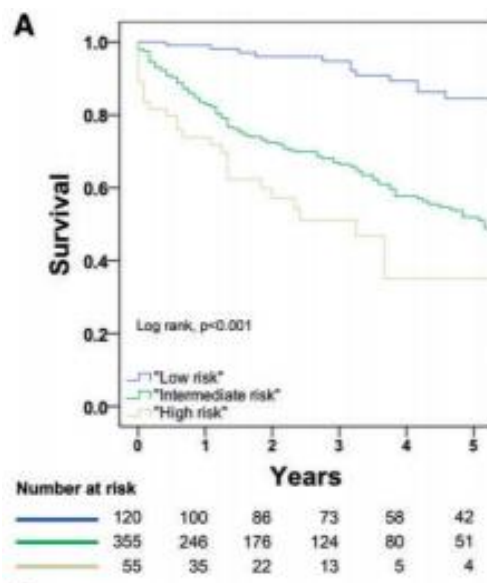
Risk scores range from 0 (lowest risk) to 22 (highest risk)

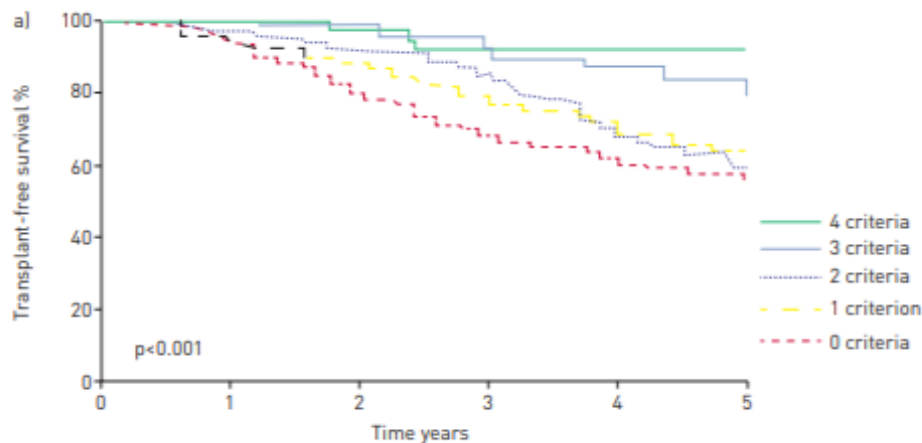
	LOW RISK	AVERAGE RISK	MODERATE HIGH RISK	HIGH RISK	VERY HIGH RISK
RISK SCORE	1–7	8	9	10–11	≥12
PREDICTED 1-YEAR SURVIVAL	95%–100%	90%–<95%	85%–<90%	70%–<85%	<70%

The SPAHR registry

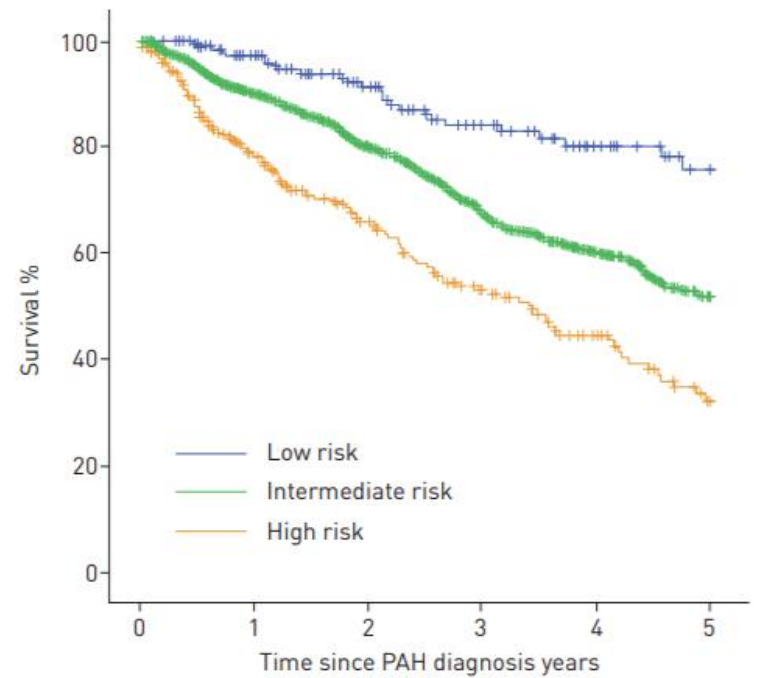
Table I Included variables from the risk assessment instrument from the ESC/ERS 2015 guidelines for the diagnosis and treatment of pulmonary hypertension and their cut-off values

Determinants of prognosis	Low risk	Intermediate risk	High risk
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
NT-proBNP levels	<300 ng/L	300–1400 ng/L	>1400 ng/L
Imaging (echocardiography)	RA area <18 cm ² No pericardial effusion CI ≥ 2.5 L/min/m ² SvO ₂ >65%	RA area 18–26 cm ² No or minimal pericardial effusion CI 2.0–2.4 L/min/m ² SvO ₂ 60–65%	RA area >26 cm ² Pericardial effusion CI <2.0 L/min/m ² SvO ₂ <60%





Patients at risk n						
4 criteria	59	52	46	35	26	20
3 criteria	112	94	74	59	36	26
2 criteria	217	173	149	104	63	45
1 criterion	371	302	233	176	128	89
0 criteria	258	212	158	117	76	53



□ Low risk criteria

- WHO FC: I or II,
- 6MWD >440 m,
- RAP <8 mmHg
- $CI \geq 2.5 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$
- $SvO_2 >65 \%$

Years after enrolment	Survival %			Cases left n		
	Low risk	Intermediate risk	High risk	Low risk	Intermediate risk	High risk
0	100	100	100	196	1116	276
1	97.2	90.1	78.8	156	764	170
2	91.5	80.3	66.0	111	540	117
3	84.2	68.1	53.2	75	376	77
4	80.2	60.1	44.7	47	252	47
5	75.9	51.9	32.4	31	149	24

The RAFi

Low risk criteria:

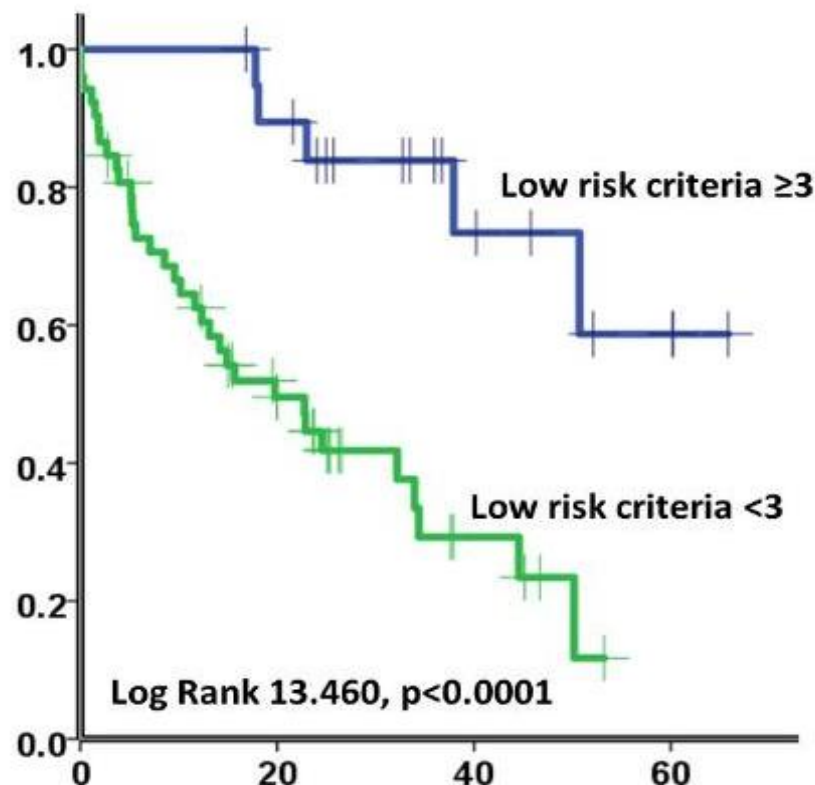
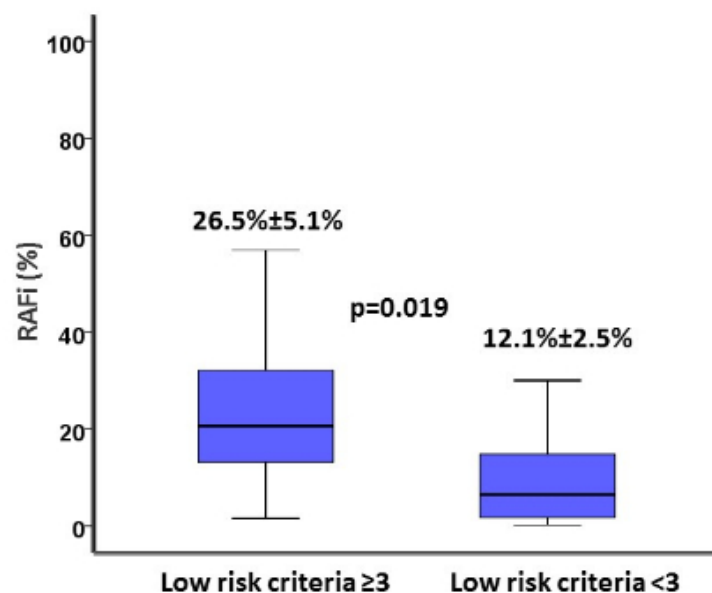
WHO FC I/II

6MWD >440 m,

RAP <8 mmHg,

CI >2.5 L·min⁻¹·m⁻²

NT-proBNP <300pg/dl





ESC/ERS 2015 Guidelines

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



6th World Symposium on PH

	Prognostic criteria	Low risk	Intermediate risk	High risk
A	WHO FC	I/II	III	IV
B	6MWD	>440m	300-440m	<165m
C	NT-proBNP Or RA	<8mmHg	300-1400ng/ml Or 8-14mmHg	>1400ng/ml Or >14mmHg
D	CI Or SvO ₂	≥ 2.5 Or >65%	2.0-2.4 Or 60-65%	<2.0 Or <60%

No place for echo?



Take home messages

- ❑ Echocardiography is the most studied imaging modality in PAH providing useful information on risk stratification and prognosis in PAH patients
- ❑ Right heart function and dimensions and pericardial effusion are the most studied main determinants of prognosis in PAH
- ❑ Right atrial function is an emerging field in the assessment of PAH prognosis
- ❑ Novel imaging techniques may be proved of prognostic significance in PAH

Acknowledgements

AHEPA University Hospital

Pulmonary Hypertension Unit



Thank you

Power of resting echocardiographic measurements to classify pulmonary hypertension patients according to European society of cardiology exercise testing risk stratification cut-offs

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