



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Pulmonary Hypertension (for the General Internist)

Aaron B. Waxman, MD, PhD

Executive Director, Center for Pulmonary Heart Diseases

Director, Pulmonary Vascular Disease Program

Pulmonary Critical Care Medicine

Brigham and Women's Hospital

Associate Professor of Medicine, Harvard Medical School



Aaron B Waxman, MD, PhD



Yale School of Medicine
Medicine Residency @ Yale New Haven Hospital
Pulmonary Critical Care Medicine Fellowship @YSM
Associate Professor of Medicine@ HMS
Director, Pulmonary Vascular Disease Program
@BWH

- Clinical focus: Pulmonary vascular disease, right heart failure, unexplained exertional intolerance
- Research focus: Mechanisms of pulmonary vascular remodeling

DISCLOSURES

- United Therapeutics – Investigator, Steering Committee member
- Merck – Investigator, and Steering Committee member
- Tectonic – Investigator and Steering Committee member
- 35Pharma – Investigator and Safety and Escalation Committee member
- Insmed – Chair, DSMB
- OrphAI – Investigator Initiated Grant
- R01HL158077
- R01HL160025
- 1UG3HL180990



Objective

Review	Review the classification of pulmonary hypertension
Review	Review the evaluation of a patient with suspected pulmonary hypertension
Review	Review the current approach to treatment



Case 1-PAH

33 yo woman G₂P_{1(5-yo male)}Sab₁ with a history of Raynaud's
3-year history of DOE, more rapidly progressing 6-months prior to
presentation

Treated for asthma with LABA / ICS without change

- Multiple steroid tapers without effect

1 month prior to presentation, pre-operative CXR (for gyn surgery) revealed
enlarged pulmonary arteries

Very symptomatic when climbing stairs or an incline



Case 1-PAH

Past Medical History

- Raynaud's
- "Asthma"

Family History

- No pulmonary or cardiac disease

Social History

- No history of smoking, alcohol, recreational drug, or anorexigens / stimulants use

Medications - none

HR: 113 SBP: 109 / 78 mmHg

O₂ saturation: 93% (RA)

No JVD

Bibasilar soft rales at the bases

Normal 1st heart sound but louder 2nd heart sound and no audible murmurs

2+ peripheral edema



When to Suspect PAH

Early

Symptoms

- Dyspnoea on exertion (WHO-FC)
- Fatigue and rapid exhaustion
- Dyspnoea when bending forward (bendopnoea)
- Palpitations
- Haemoptysis
- Exercise-induced abdominal distension and nausea
- Weight gain due to fluid retention
- Syncope (during or shortly after physical exertion)

Rare symptoms due to pulmonary artery dilation^a

- Exertional chest pain:
dynamic compression of the left main coronary artery
- Hoarseness (dysphonia):
compression of the left laryngeal recurrent nerve
(cardiovocal or Ortner's syndrome)
- Shortness of breath, wheezing, cough, lower respiratory tract infection, atelectasis:
compression of the bronchi

Late

Signs of PH

- Central, peripheral, or mixed cyanosis
- Accentuated pulmonary component of the second heart sound
- RV third heart sound
- Systolic murmur of tricuspid regurgitation
- Diastolic murmur of pulmonary regurgitation

Signs of RV backward failure

- Distended and pulsating jugular veins
- Abdominal distension
- Hepatomegaly
- Ascites
- Peripheral oedema

Signs pointing towards underlying cause of PH

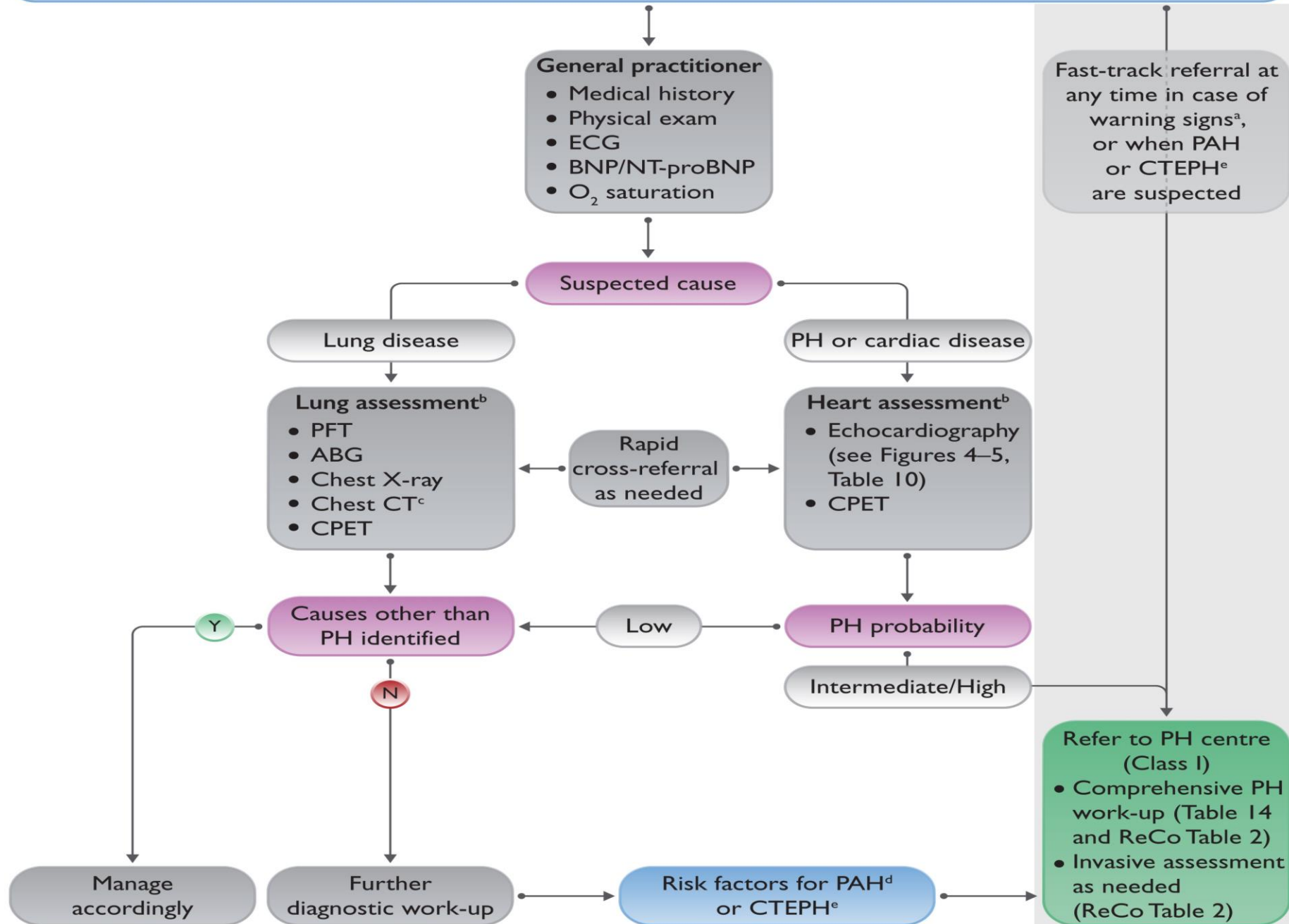
- Digital clubbing: Cyanotic CHD, fibrotic lung disease, bronchiectasis, PVOD, or liver disease
- Differential clubbing/cyanosis: PDA/Eisenmenger's syndrome
- Auscultatory findings (crackles or wheezing, murmurs): lung or heart disease
- Sequelae of DVT, venous insufficiency: CTEPH
- Telangiectasia: HHT or SSc
- Sclerodactyly, Raynaud's phenomenon, digital ulceration, GORD: SSc

Signs of RV forward failure

- Peripheral cyanosis (blue lips and tips)
- Dizziness
- Pallor
- Cool extremities
- Prolonged capillary refill



Diagnostic algorithm of patients with unexplained exertional dyspnoea and/or suspected PH



33 yo Woman with Dyspnea

Female
67in
Room:909
Loc:206

Caucasian
224lb

Vent. rate	94	BPM
PR interval	220	ms
QRS duration	120	ms
QT/QTc	576/720	ms
P-R-T axes	26 122 24	
BP	88/48	mmHg

Sinus rhythm with 1st degree A-V block

Right axis deviation

Right atrial enlargement

Abnormal ECG

When compared with ECG of 23-APR-2023 05:04, (unconfirmed)

Non-specific change in ST segment in Lateral leads

Nonspecific T wave abnormality, improved in Lateral leads

QT has lengthened

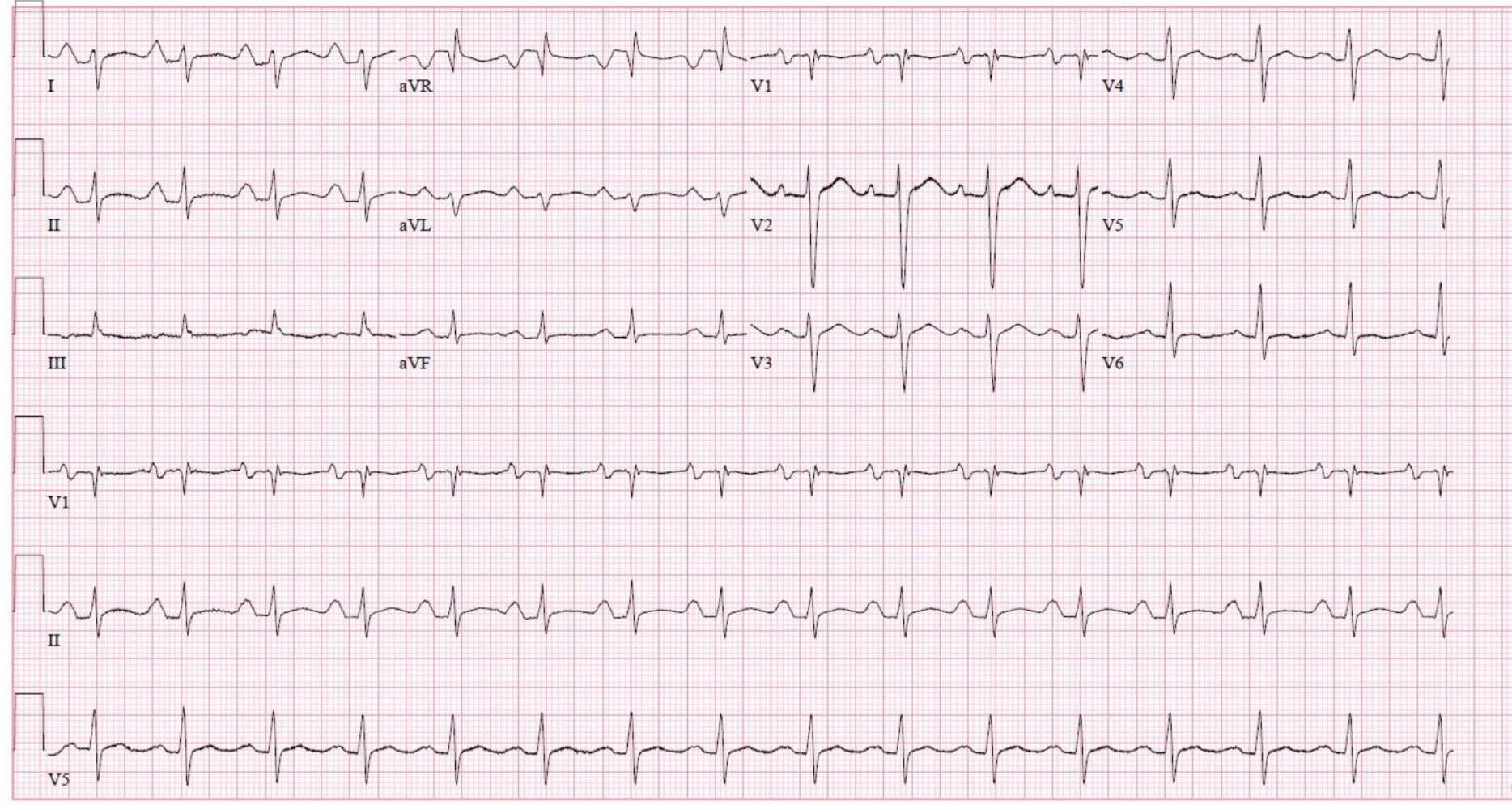
Electronically signed by ROSENBAUM M.D., LISA (519) on 4/24/2023 6:09:54 PM

Technician: System System
Test ind: 149.9

Referred by: ELAZER EDELMAN

Confirmed By: LISA ROSENBAUM M.D.

F Number:



Case 1-PAH

Pulmonary Function Tests

- Normal Spirometry
- Normal Lung Volumes
- Lower limit of normal DLCO

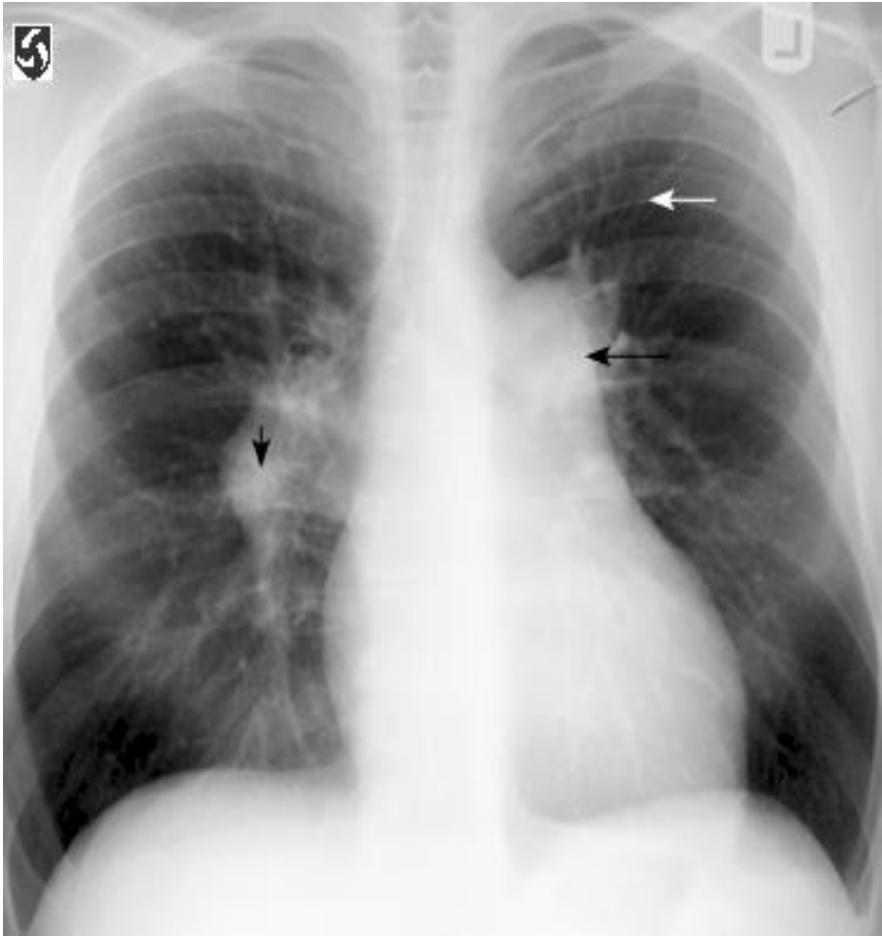
Normal metabolic profile, liver function tests, blood counts and thyroid function tests

NT-proBNP - 1836

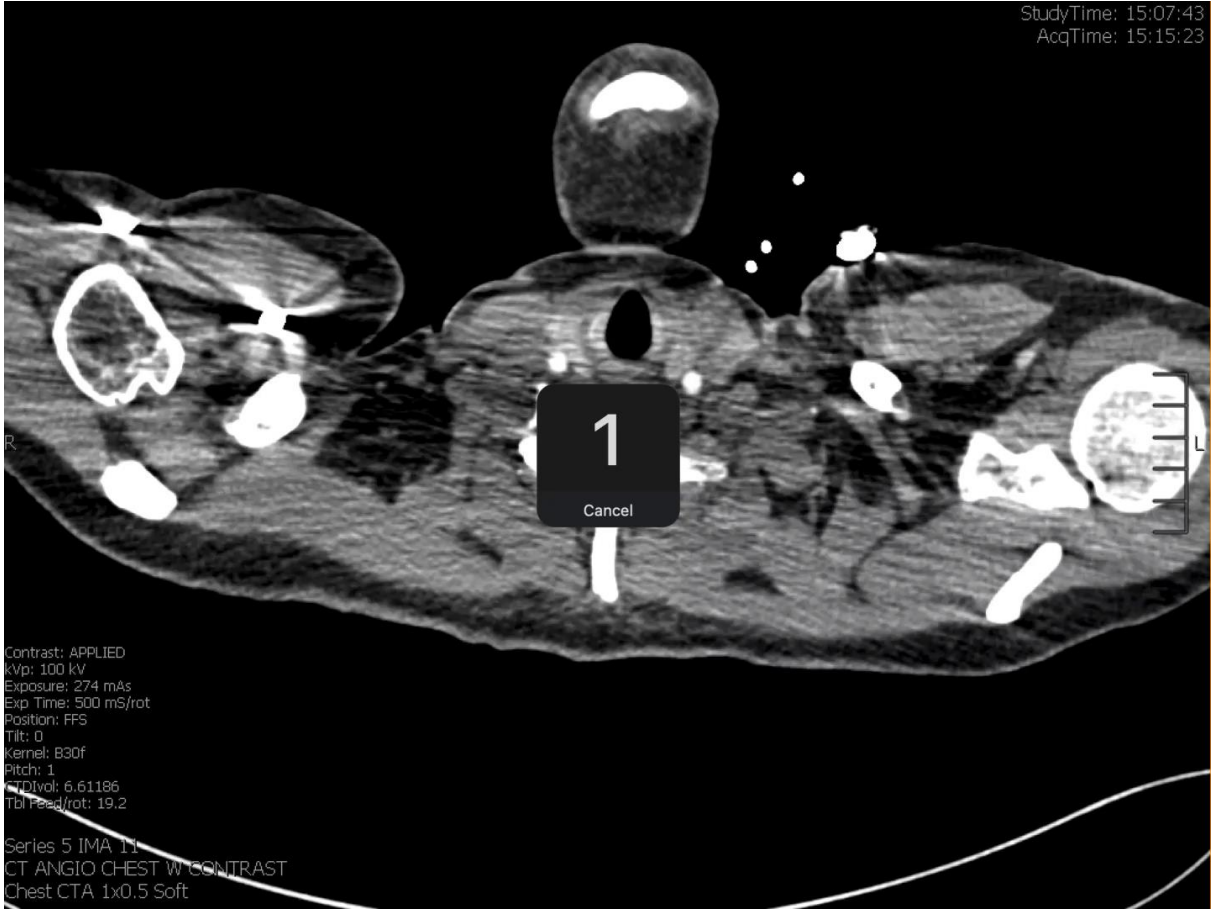
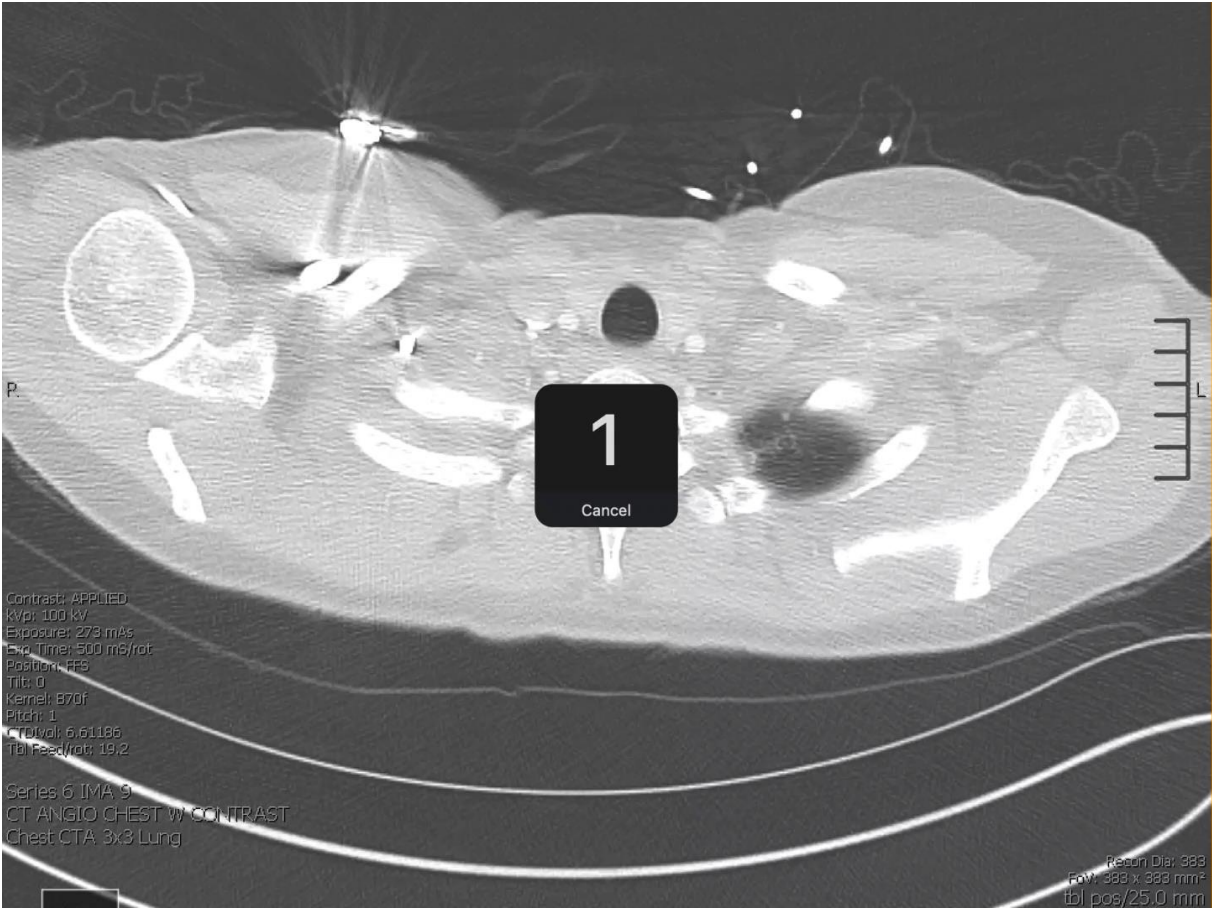
ANA + 1:320 and other auto-immune serology's negative



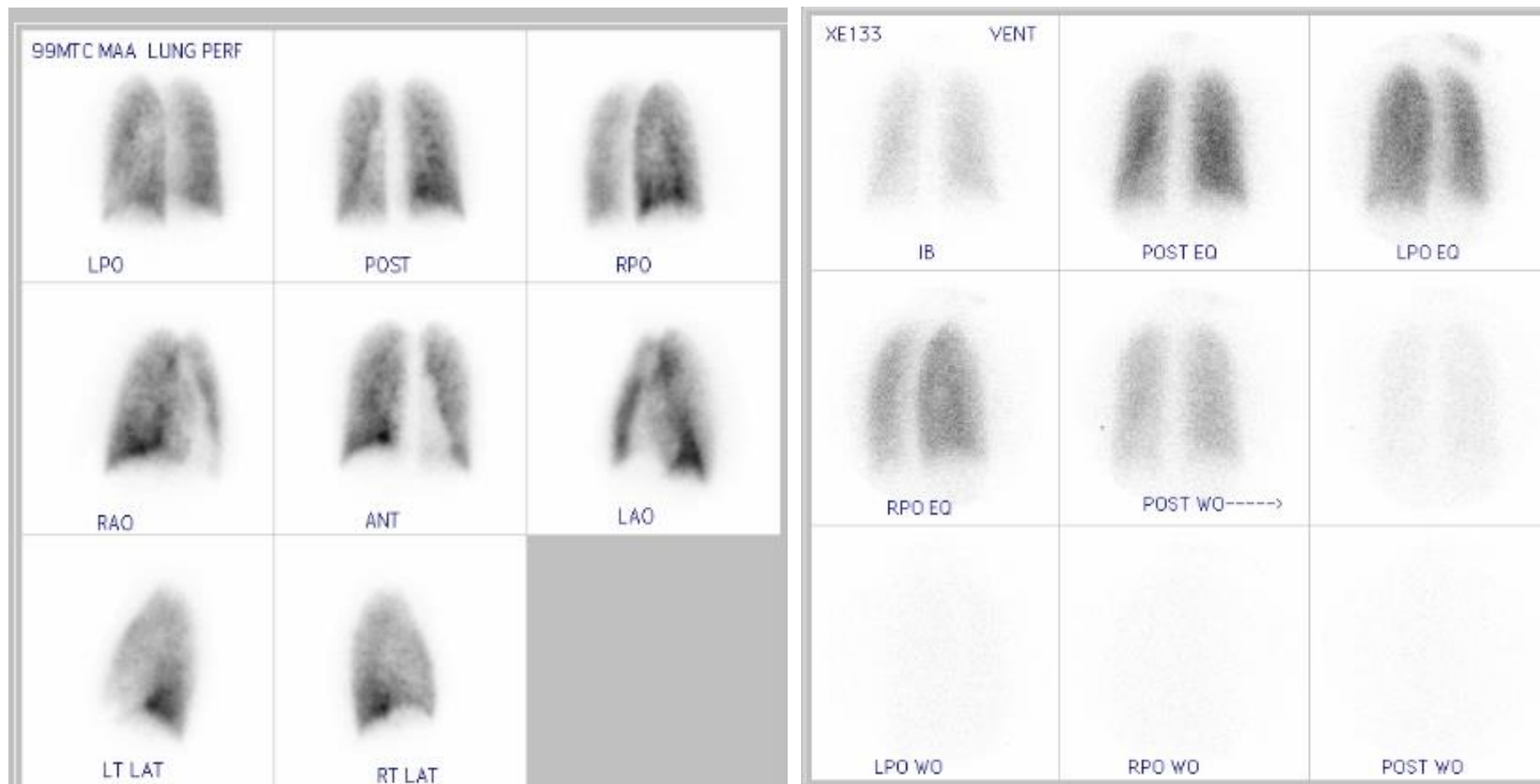
Chest Radiograph



CTA



VQ Scan



Patient #1: Physical Examination

Six Minute Walk

- 318 meters Borg 5
- Desaturations to 89% during 6MW

Chest CT

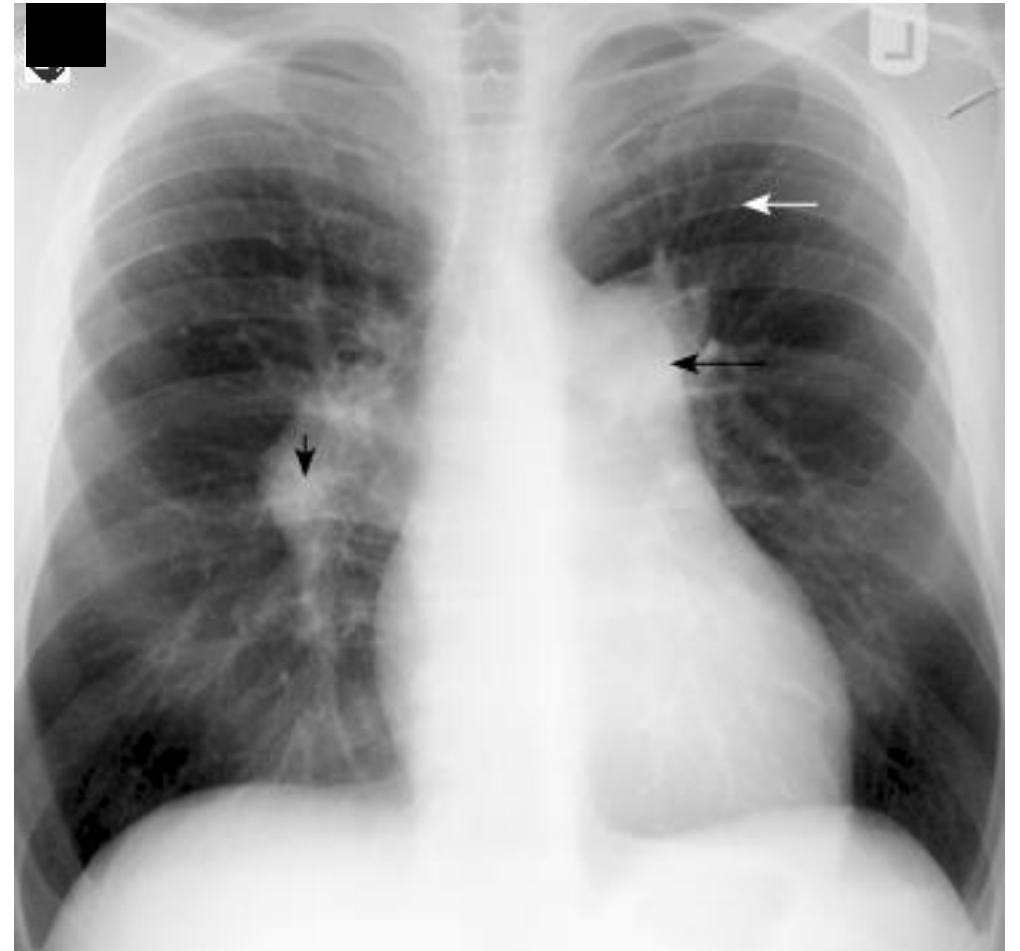
- No signs of interstitial lung disease or pulmonary emboli

V/Q scan

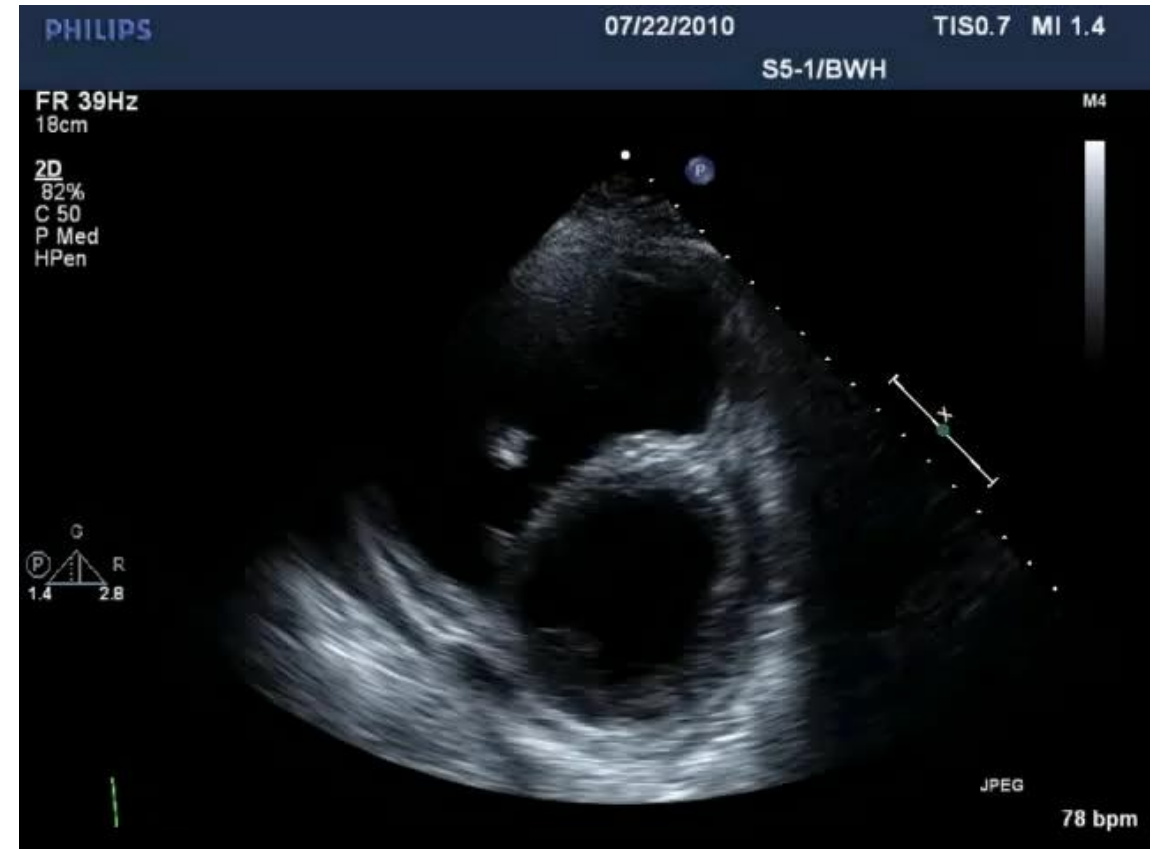
- No evidence of large obstructive clot

EKG

- RAD, RVH, P-pulmonale

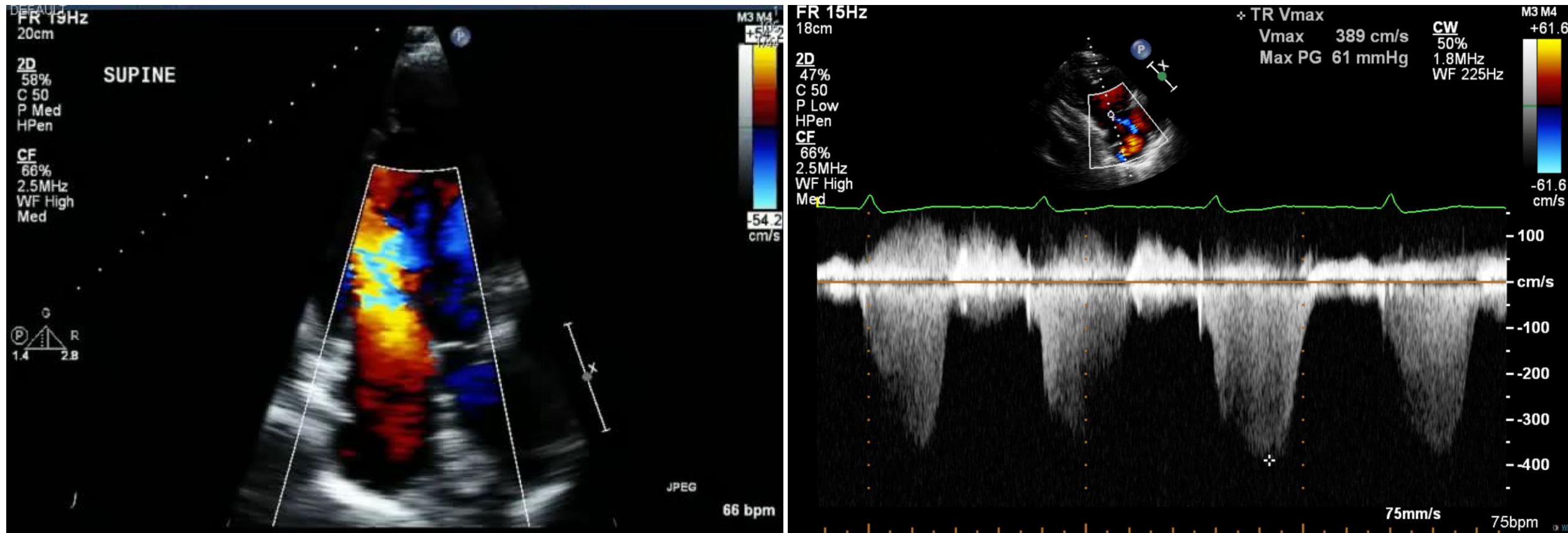


33 yo Woman with Dyspnea

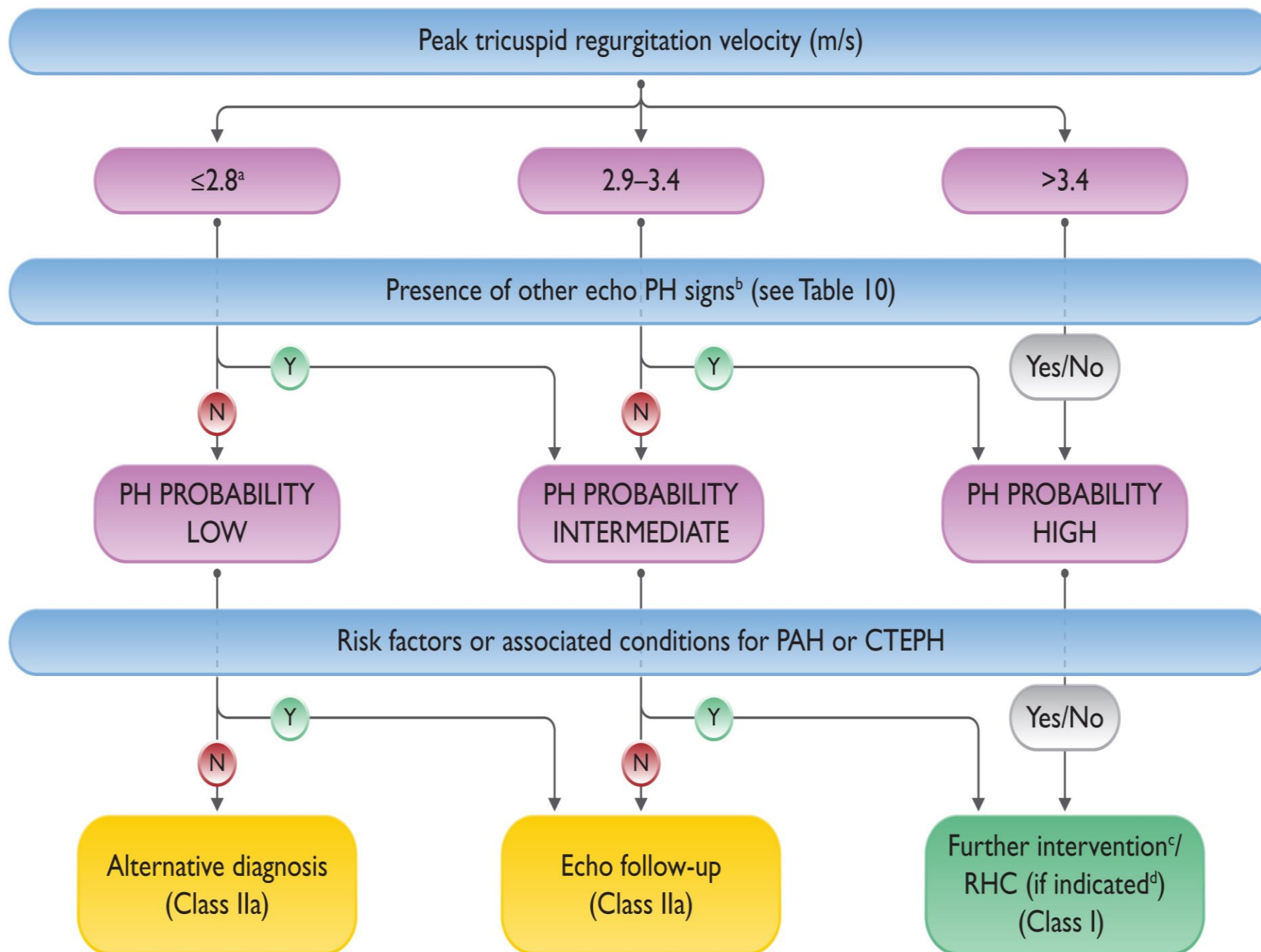


33 yo Woman with dyspnea

Tricuspid Regurgitation



Modified Bernoulli's Equation:
 $4 \times (V)^2 + RAP = RVSP (PASP)$
 $RVSP \sim 78$



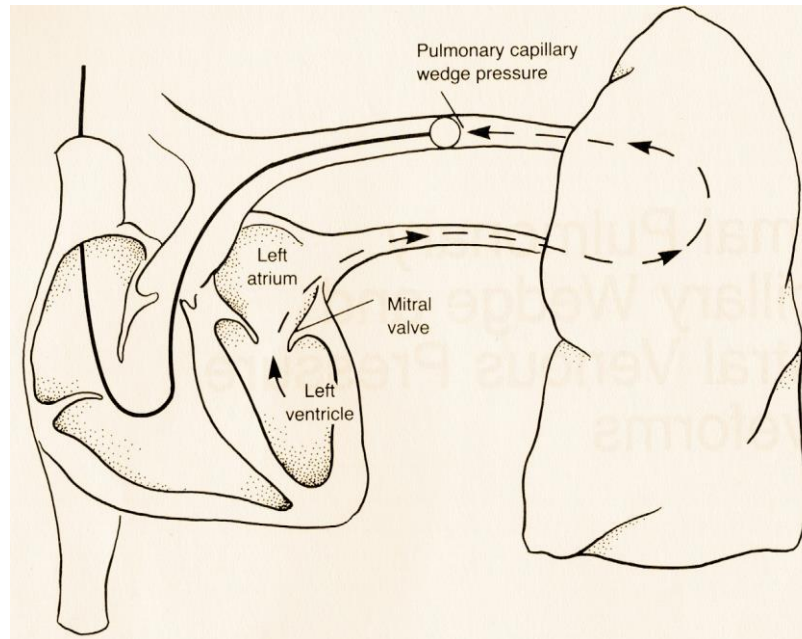
Information obtained from the PAC

Directly measured

- CVP
- PA pressure
- PCWP
- Cardiac output
- SvO_2

Calculated from directly measured data

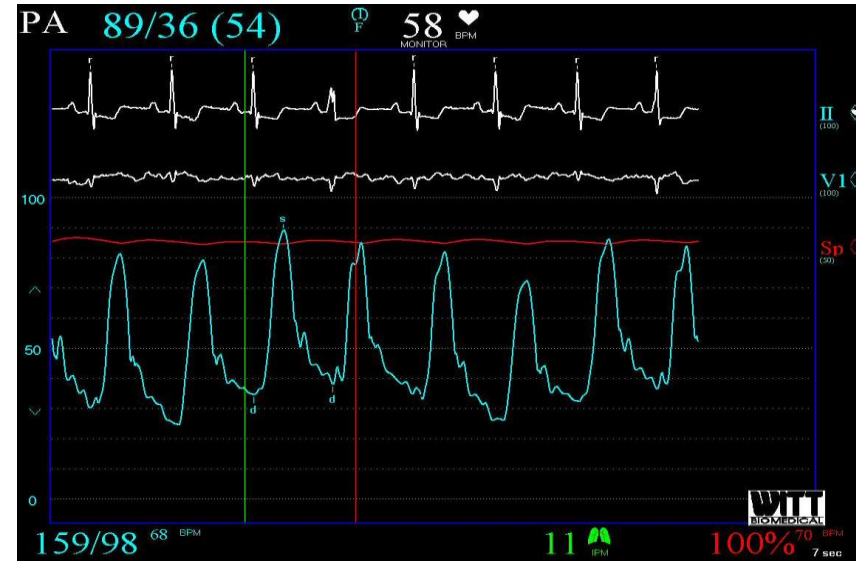
- Stroke volume / index
- Cardiac index
- Systemic vascular resistance
- Pulmonary vascular resistance
- Oxygen delivery



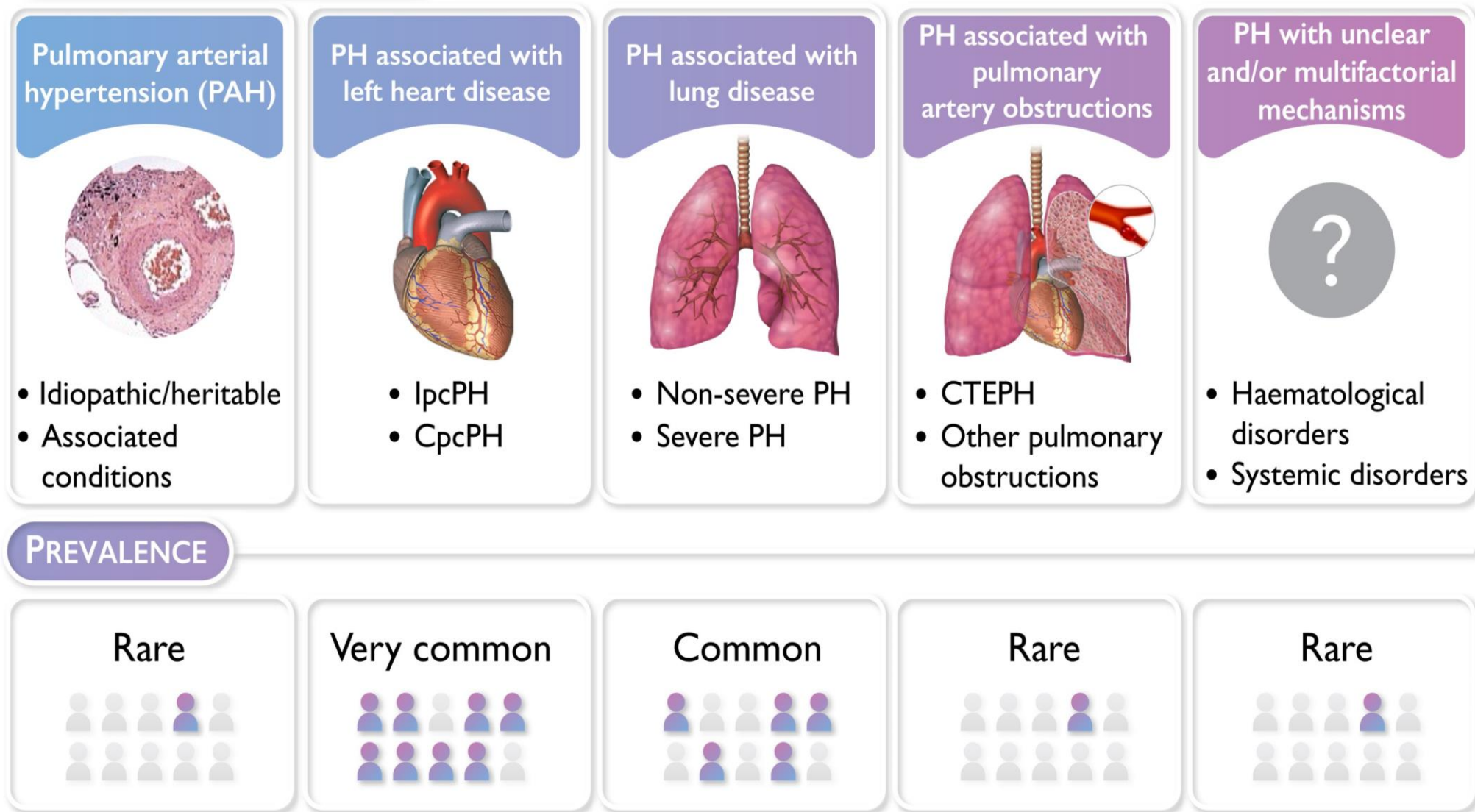
Case 1-PAH

RHC:

- RA (CVP) 17
- RV 87/12 (RVEDP: 21)
- PAP 89/36 (54)
- PCWP 14
- CO/CI 4.6/1.8
- PVR 710 (9wu); SVR 871
- 40ppm NO – No response



Updated Classification System



Case 1-PAH



Severe PAH, NYHA Functional Class 3b

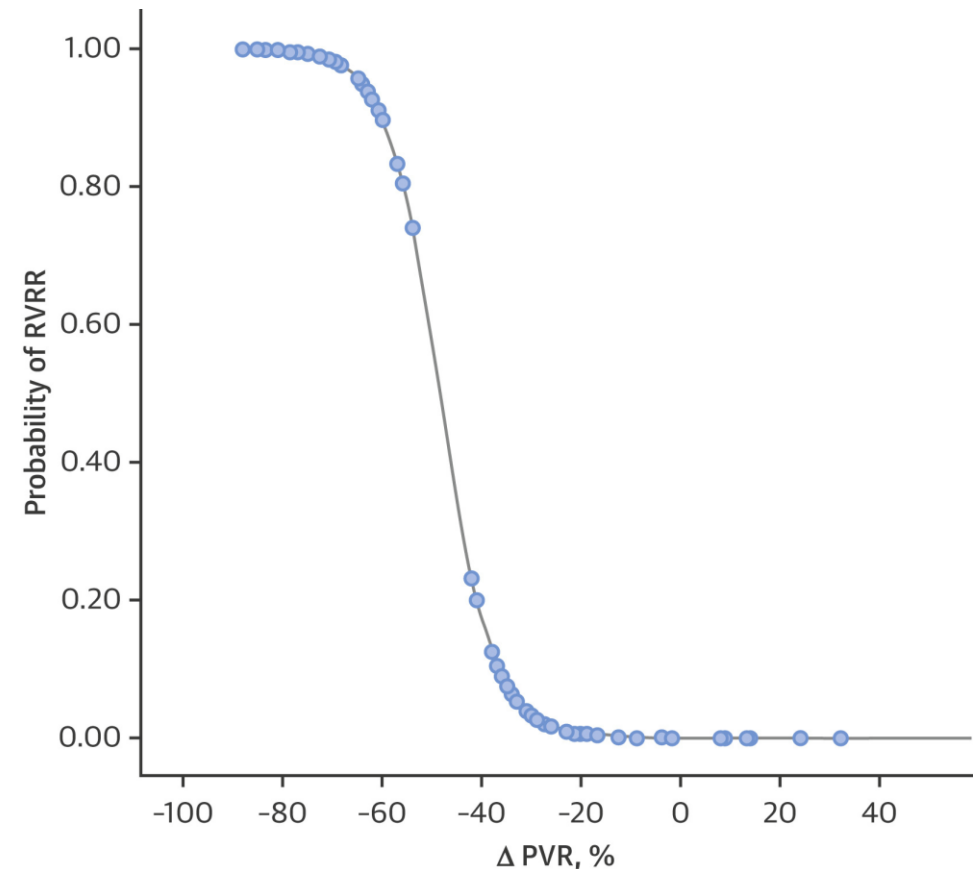
- HR 113
- SBP 109
- 6-MWD 318m, BDS 5
- NT-proBNP – 1836
- REVEAL Score >8

How do we treat this patient?

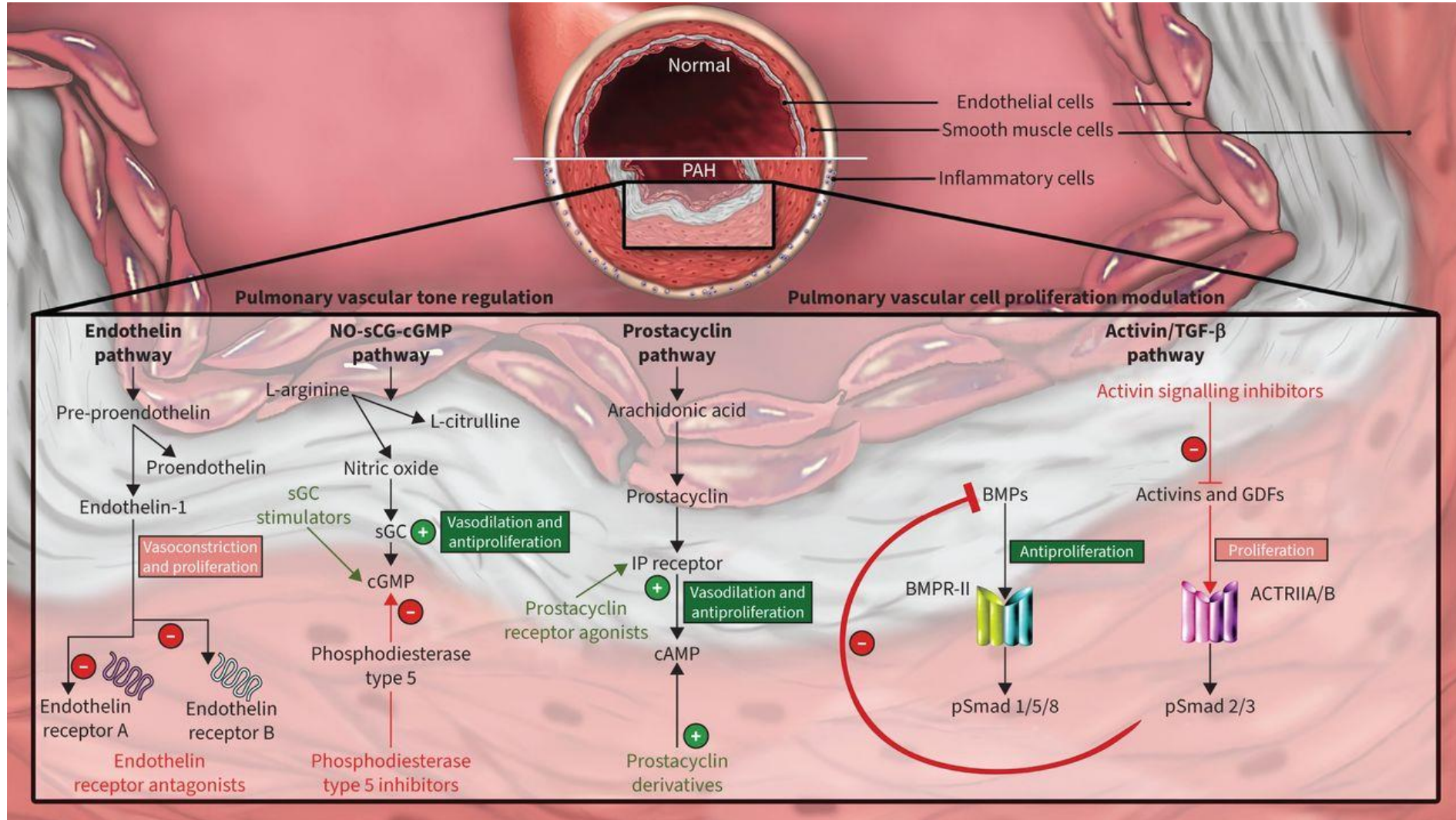
How do we monitor and follow-up this patient ?

Pulmonary Arterial Hypertension: *Goals of Therapy*

- Improve exercise capacity
- Improve functional class
- Prevent clinical worsening
- Improve survival
- Improve hemodynamics
 - At least a 50% reduction in PVR
 - mPA < 25 mmHg



Targets for established and emerging therapies in pulmonary arterial hypertension



Pulmonary Vascular Tone Regulation

Vascular Cell Proliferation Modulation

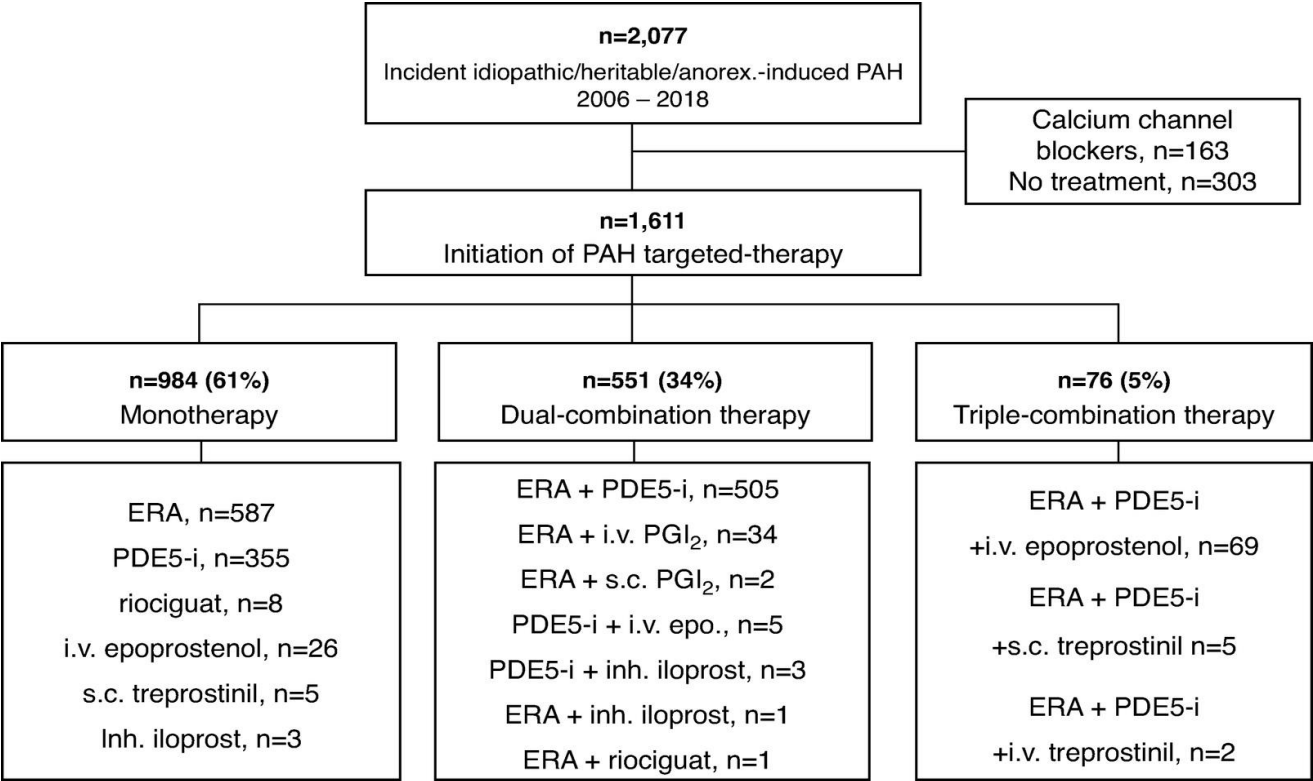
Expected Adverse Effects of PAH-Specific Therapies

Most PAH medications have class-related adverse effects, often due to vasodilatory properties of the medications

- ERAs
 - Edema
- PDE-5 inhibitors
 - Flushing, headache
- Prostacyclins
 - Headache, flushing, jaw pain, nausea
- Riociguat (sGC inhibitor)
 - Flushing, headache
- Selexipag (IP receptor agonist)
 - Headache, flushing, nausea
- Activin Inhibitors
 - Sotatercept – Increased Hgb, telangiectasias, epistaxis

In addition, PAH medications are often up-titrated on the basis of tolerability

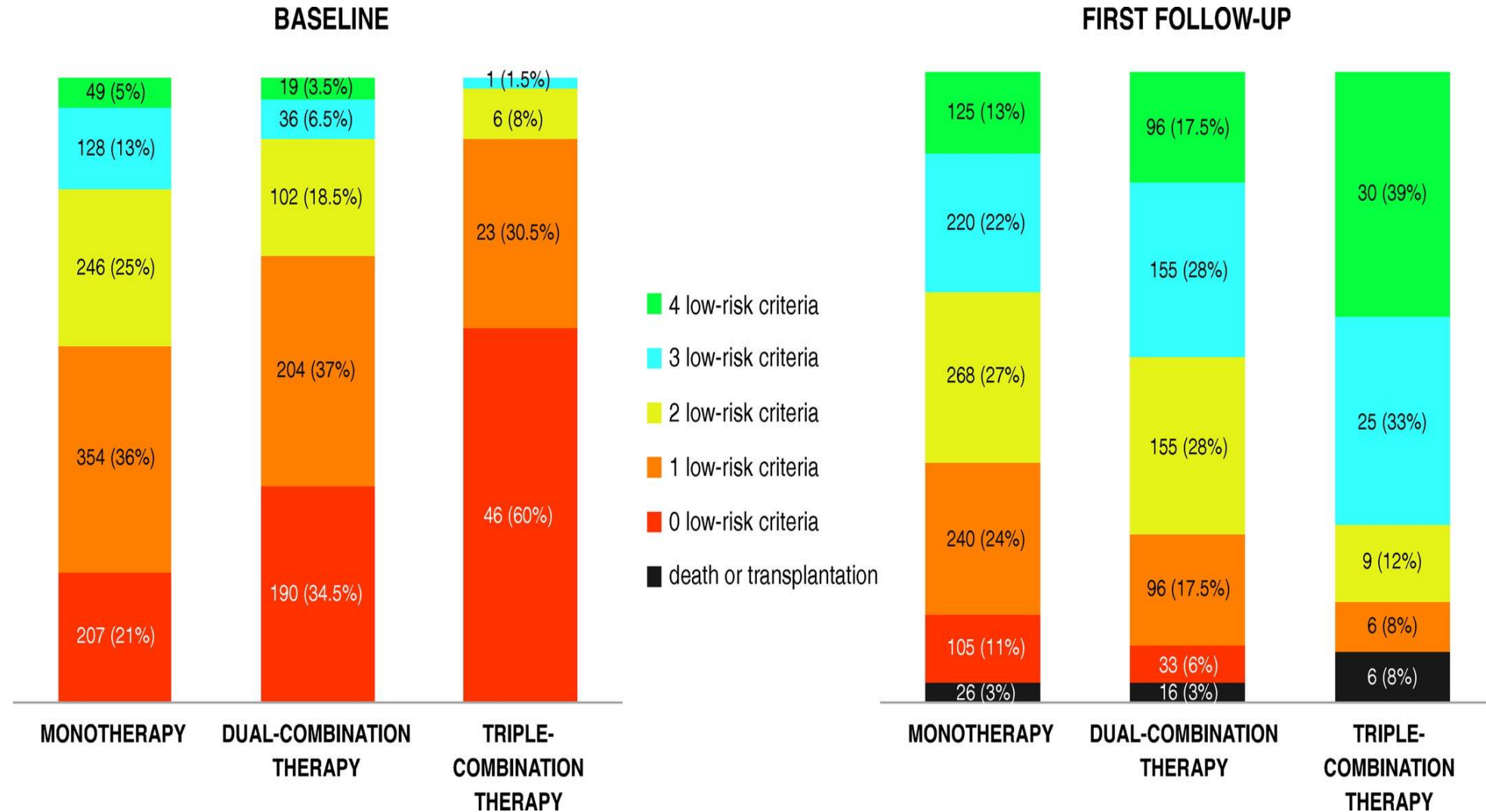
Association between Initial Treatment Strategy and Long-Term Survival in Pulmonary Arterial Hypertension



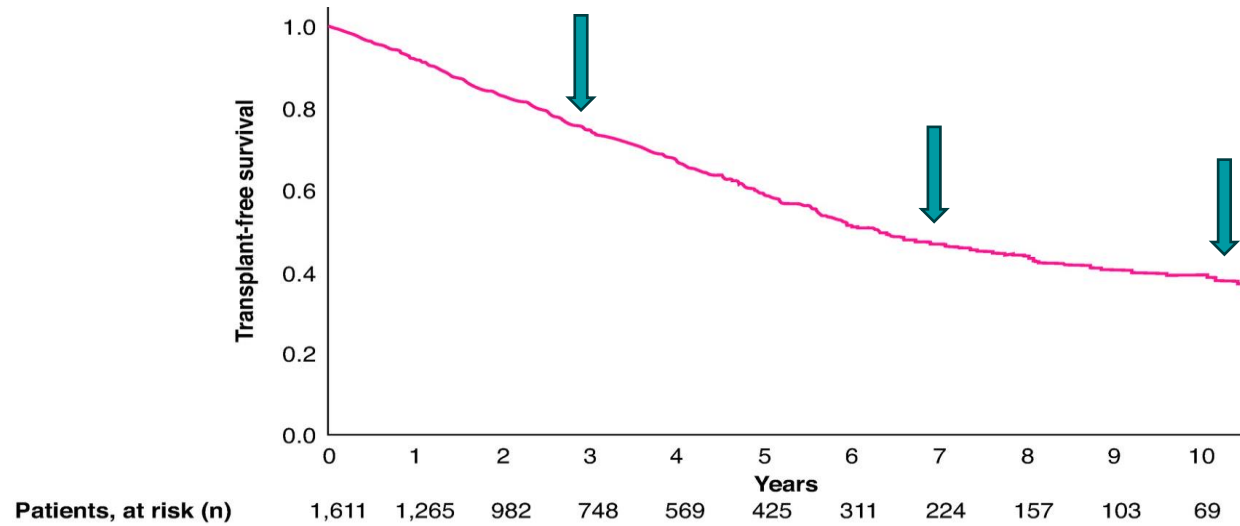
Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II ^a	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP, ^a ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

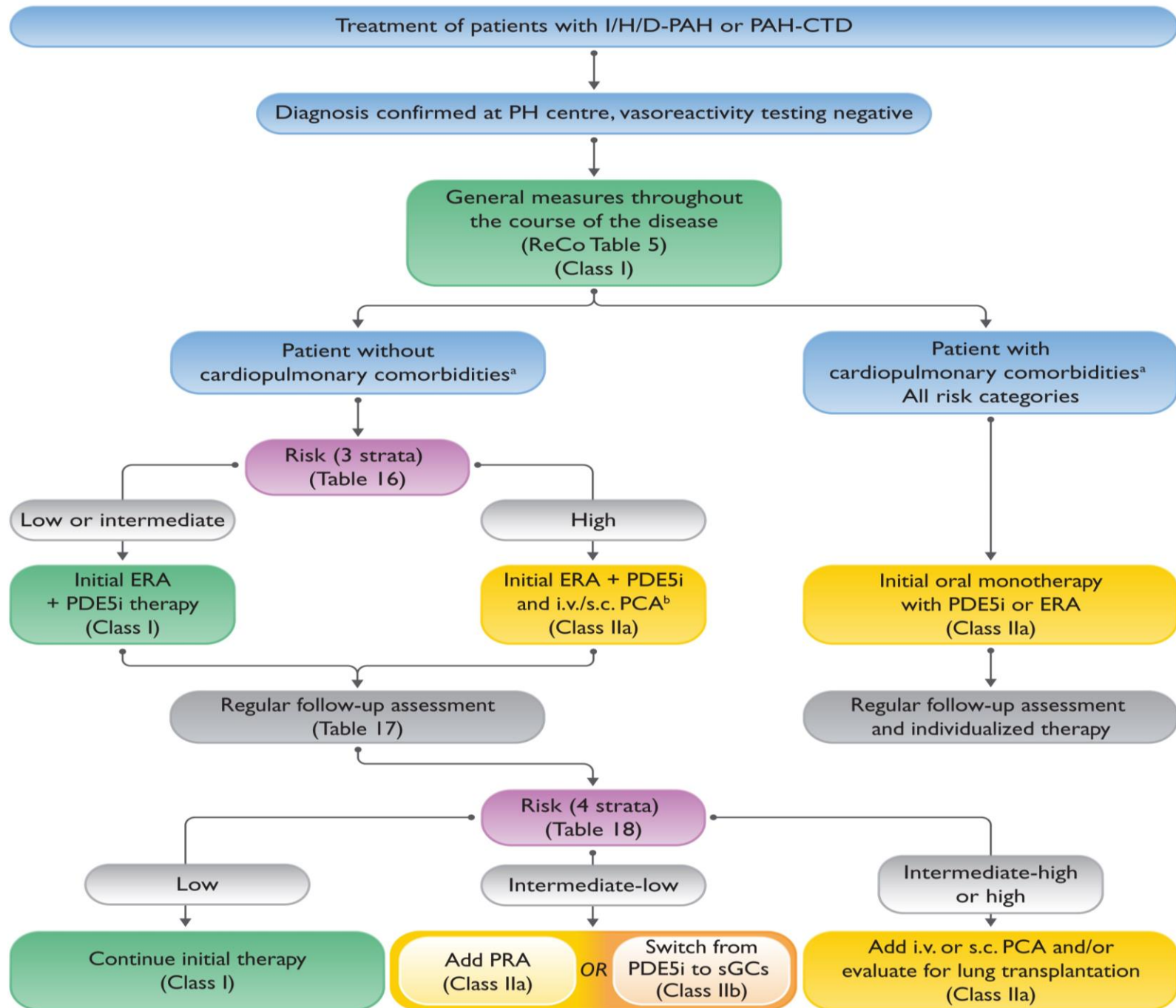


Association between Initial Treatment Strategy and Long-Term Survival in Pulmonary Arterial Hypertension



Association between Initial Treatment Strategy and Long-Term Survival in Pulmonary Arterial Hypertension





Treatment Algorithm

General Measures	Supportive Therapy
• Avoid pregnancy • Influenza and pneumococcal immunization • Psychological counseling • Supervised exercise training • Supplemented oxygen • Regional anesthesia preferred over general anesthesia	• Diuretics • Long-term oxygen therapy • Anticoagulant therapy • Iron deficiency correction • Use of ACEi, AT1-antagonists, β-blockers, ivabradine only if specifically indicated • Treatment of arrhythmias

Note: **Oral anticoagulant therapy is not recommended in associated forms of PAH, while in IPAH, HPAH and DT-PAH the data on efficacy is more conflicting.** The decision about anticoagulation has to be made on a case-by-case basis after an individual risk–benefit analysis.

Follow-up Monitoring Schedule

Parameter	Baseline (pretreatment)	Every 3-6 months	3-4 Months after start or change in therapy	If clinical worsening
Clinical assessment WHO functional class ECG	X	X	X	X
6-MWD / CPET	X	X	X	X
BNP / NT-proBNP	X	X	X	X
ECHO	X		(X)	X
Right heart catheterization	X		(X)	X



Case 1-PAH

Severe PAH, NYHA Functional Class 3b

- 6-MWD 318m, BDS 5

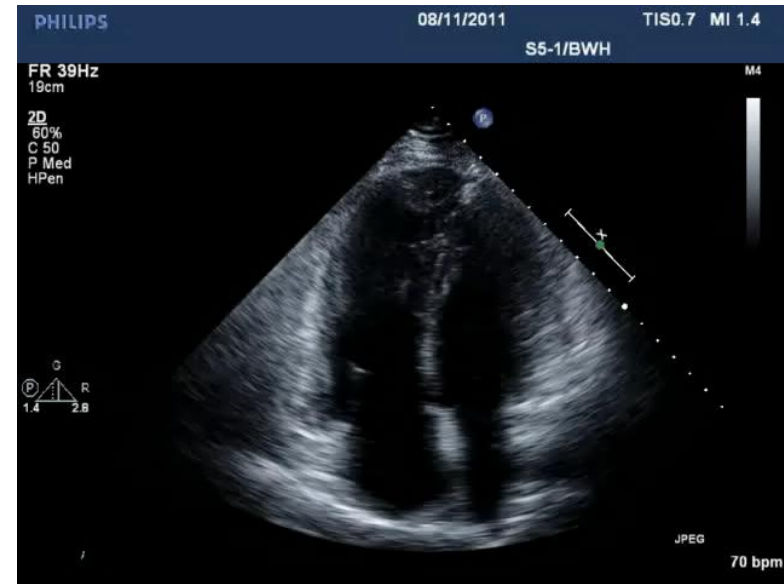
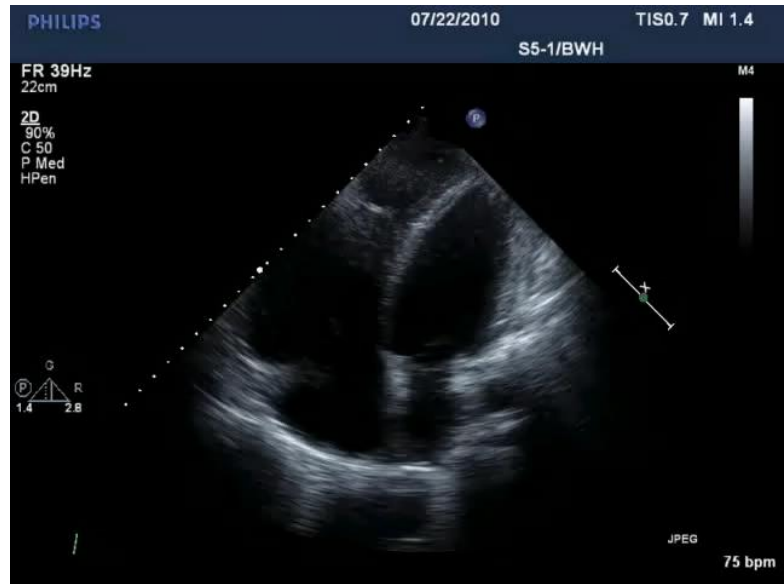
Treated with the prostacyclin analog *treprostinil* and PDE5i *tadalafil* with a good clinical response, *ambrisentan* was added two weeks later

Repeat ECHO, after 6-months demonstrated improvement in RV size and function

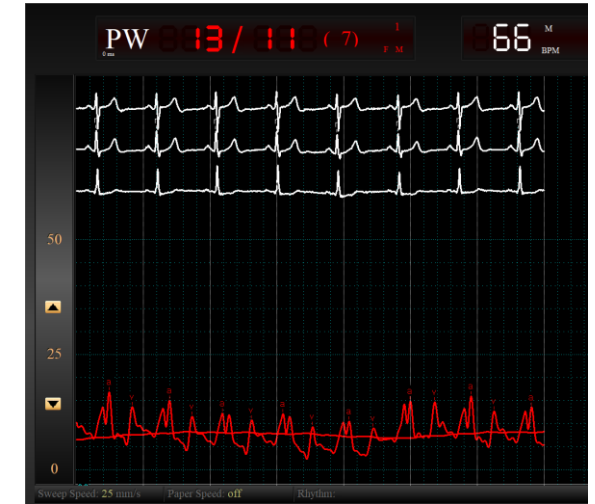
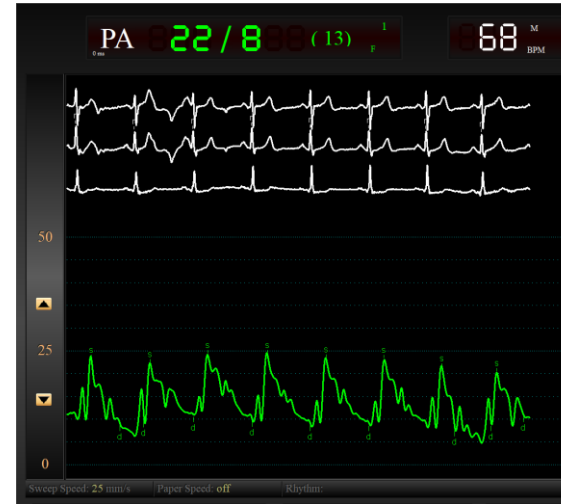
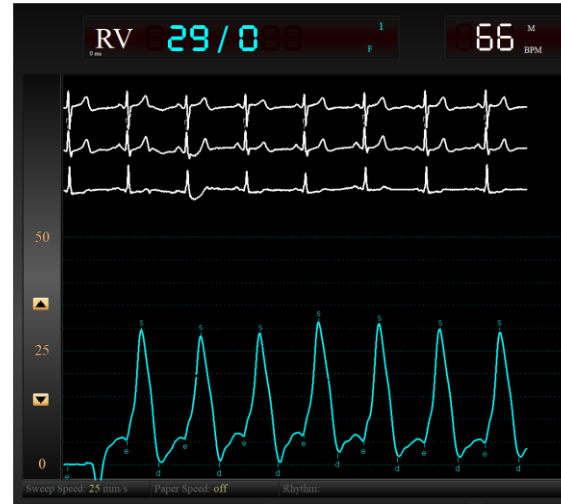
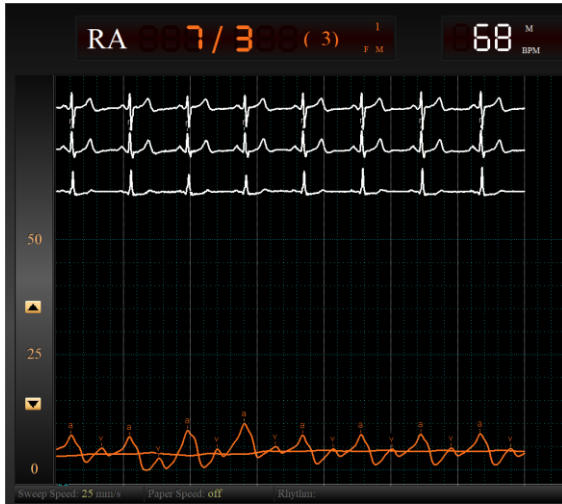
- PAsp now estimated at 72 mmHg
- 6-MWD – 448m Borg – 3
- WHO Functional Class 2



6-months later



2.5 years later



Treprostinil titrated to 66 ng/kg/min
Ambrisentan 10mg daily
Tadalafil 20mg tablets 2-tablets daily
Participant in SPECTRA study of Sotatercept
WHO FC 1

- RHC:
 - PAP 22/8
 - mPA 13
 - PCWP 7
 - CO/CI 5.6/2.8
 - PVR 1.5 Wu



Summary - MOC REFLECTIVE STATEMENT

- Cardiac Echo is an excellent screening tool, but does not provide a diagnosis
- RHC is *essential and required* for diagnosis of all forms of pulmonary hypertension
- With development of new therapies, we are seeing improved outcomes
- Outcomes provide a clear rational for combination therapy
- Treatment must be individualized to not only severity but to patient preference and lifestyle
- There is still plenty of room for additional therapeutic targets



References

Molecular Mechanisms of Pulmonary Vascular Remodeling in Pulmonary Arterial Hypertension Updated Treatment Algorithm of Pulmonary Arterial Hypertension., J. Leopold and B. Maron, *Int. J. Mol. Sci.* 2016, 17(5), 761

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SPECTRA Phase 2b Study: Impact of Sotatercept on Exercise Tolerance and Right Ventricular Function in Pulmonary Arterial Hypertension. *Circ Heart Fail.* 2024 Apr 4:e011227. doi:10.1161/CIRCHEARTFAILURE.123.011227
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