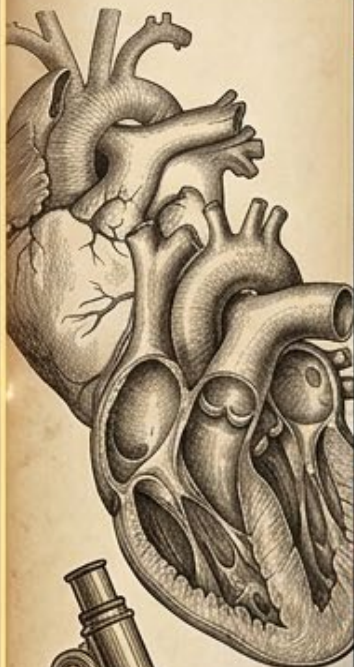
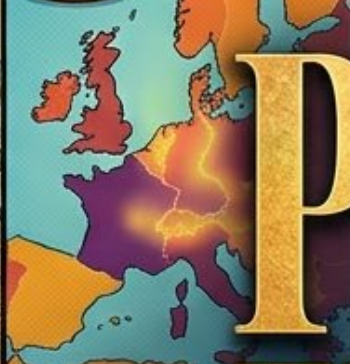


**MORBID ANATOMY**  
1891-1950s



**TOXIC TRIGGER**  
1960s



**NATURAL HISTORY**  
1980s-1990s



**ICE PACK**  
1990s



**TABLET**



**ERA** >>>

**POLYPHARMACY**  
2010s-2020s

High	High
2nd	Cochral
Low	3-strata

**MOLECULAR**  
2020s+



Targeted receptor

# PULM HTN THE ERAS TOUR

**Zachary Fulkerson, MD, PhD**  
Director of the Pulmonary Hypertension Center  
Indiana University School of Medicine



Advanced 4-strata

Low	Inter-Low	High-High	Hig
Low er-Low model	<b>GREEN ZONE</b>		
High			



# Disclosures



No financial disclosures



Artificial Intelligence (AI) technology was utilized to synthesize certain illustrations and graphic elements featured in this presentation.



All medical and scientific content remains the work and responsibility of the author.

# Objectives

1. Recognize the clinical features, risk factors, and classification of pulmonary hypertension
2. Describe the recommended diagnostic evaluation for suspected pulmonary hypertension.
3. Apply current evidence-based management strategies for the treatment of pulmonary hypertension

# Gaps/ Needs/ Outcome



Clinicians may not be aware of the history of pulmonary hypertension due to limited clinical indicators

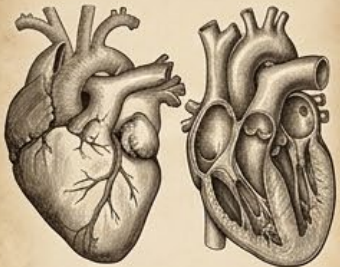


Education is necessary to improve early recognition and appropriate treatment



To improve the treatment of patients with pulmonary hypertension

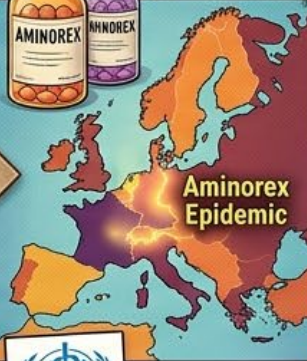
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"The right ventricle was found to be of enormous size..."  
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Aminorex Epidemic

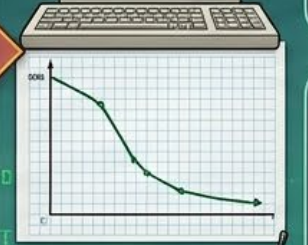


1st WHO PH Symposium (1973)

# 1980s-1990s THE NATURAL HISTORY ERA.



NIH REGISTRY:  
Median Survival without treatment ~2.8 years.



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'cold chain' logistics chain



IV EPOPROSTENOL



1995 FDA Approval

# 2000s-early 2010s THE TABLET ERA.



ERA (AMBRISENTAN)

PDE5-I (SILDENAFIL)

3-strata risk assessment

High	High
2nd	Coctnal
Low	3-strata

Sequential monotherapy VS. Upfront combo therapy

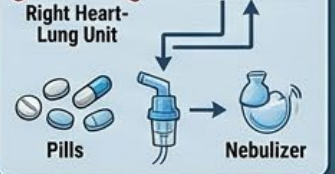
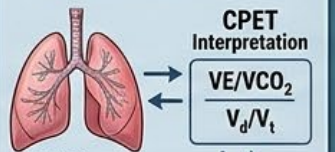
# 2010s-2020s THE POLYPHARMACY ERA.

AMBITION Trial (2015)

Ambrisentan + Tadalafil

-50% reduction in clinical failure

Right Heart-Lung Unit



# 2020s and beyond THE MOLECULAR ERA.

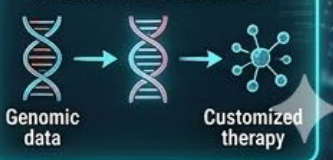


Targeted receptor

Advanced 4-strata

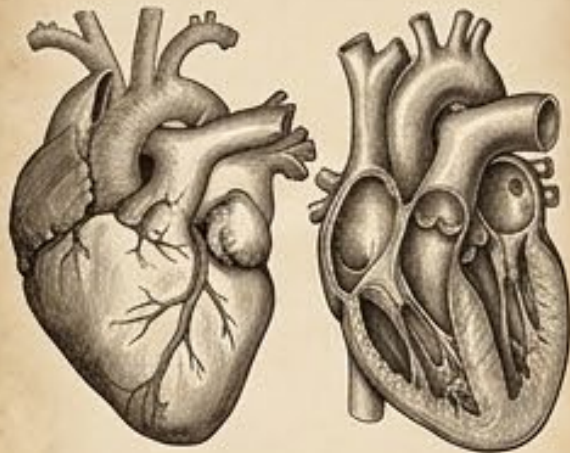
Low	Inter-Low	Inter-High	High
Low	Inter-Low model	GREEN ZONE	
High			

Personalized Medicine



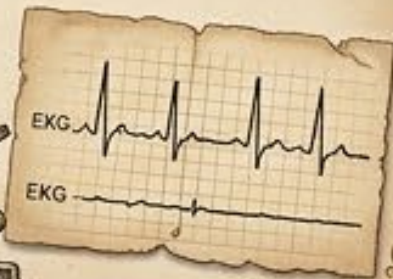
1891-1950s

# THE MORBID ANATOMY ERA.



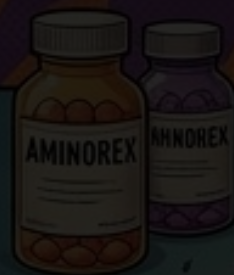
*"The right ventricle was found to be of enormous size..."*

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1960s

# THE TOXIC TRIGGER ERA.



Aminorex Epidemic



1st WHO PH Symposium (1973)

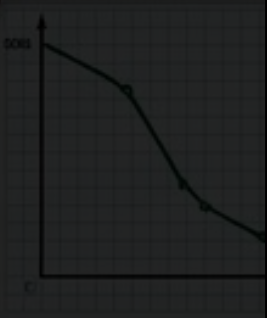


1980s-1990s

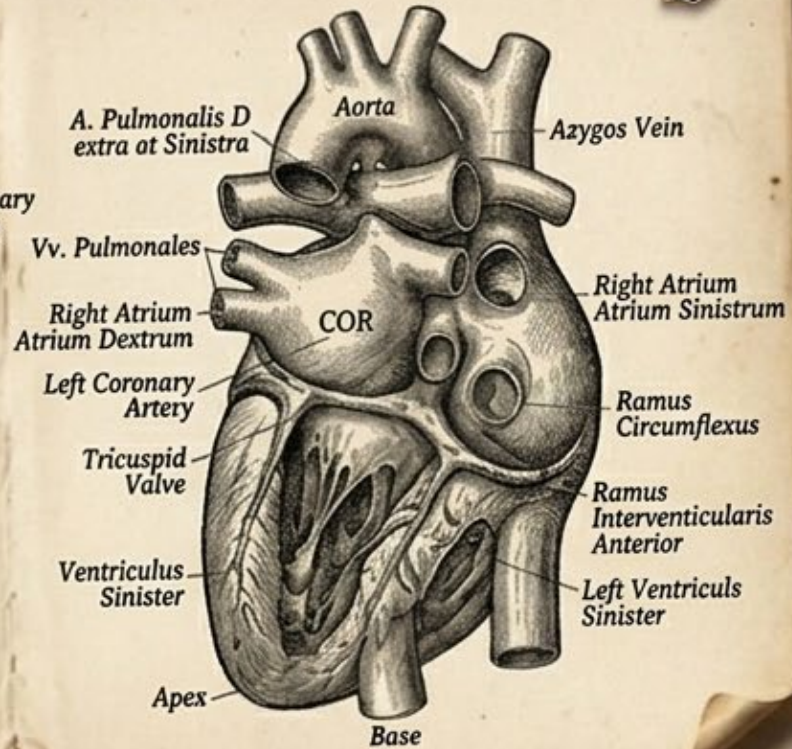
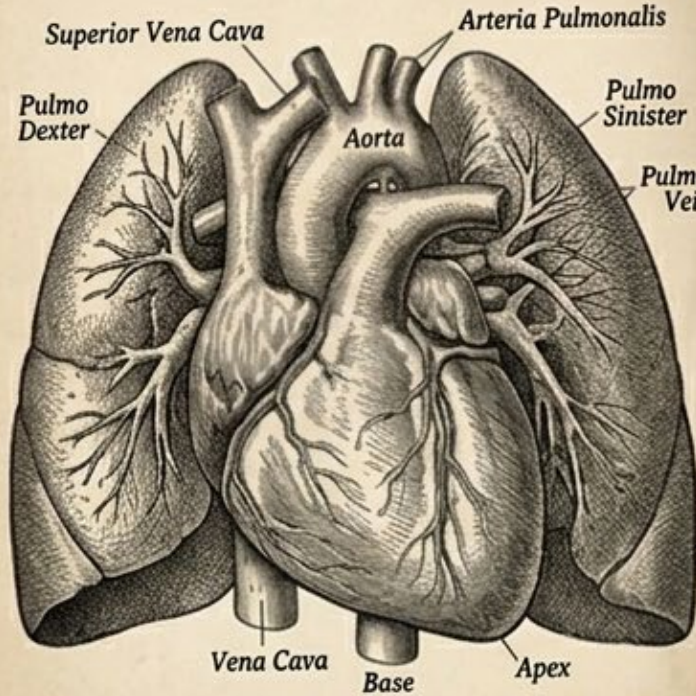
# THE NATURAL HISTORY ERA.

NIH REGISTRY

Median Survival without treatment  
~2.8 years



# 1891 -- Ernst von Romberg



# Pulmonary Vascular Sclerosis

Normal distal p  
Plexiform lesion formation  
Intimal f  
EC apoptosis an  
Inflammat  
recruitm  
Fibroblast pro  
Collagen dis  
Remodeled pul

Ernst von Romberg, 1891

Presented by Zachary Fulkerson, MD, PhD, Indiana University

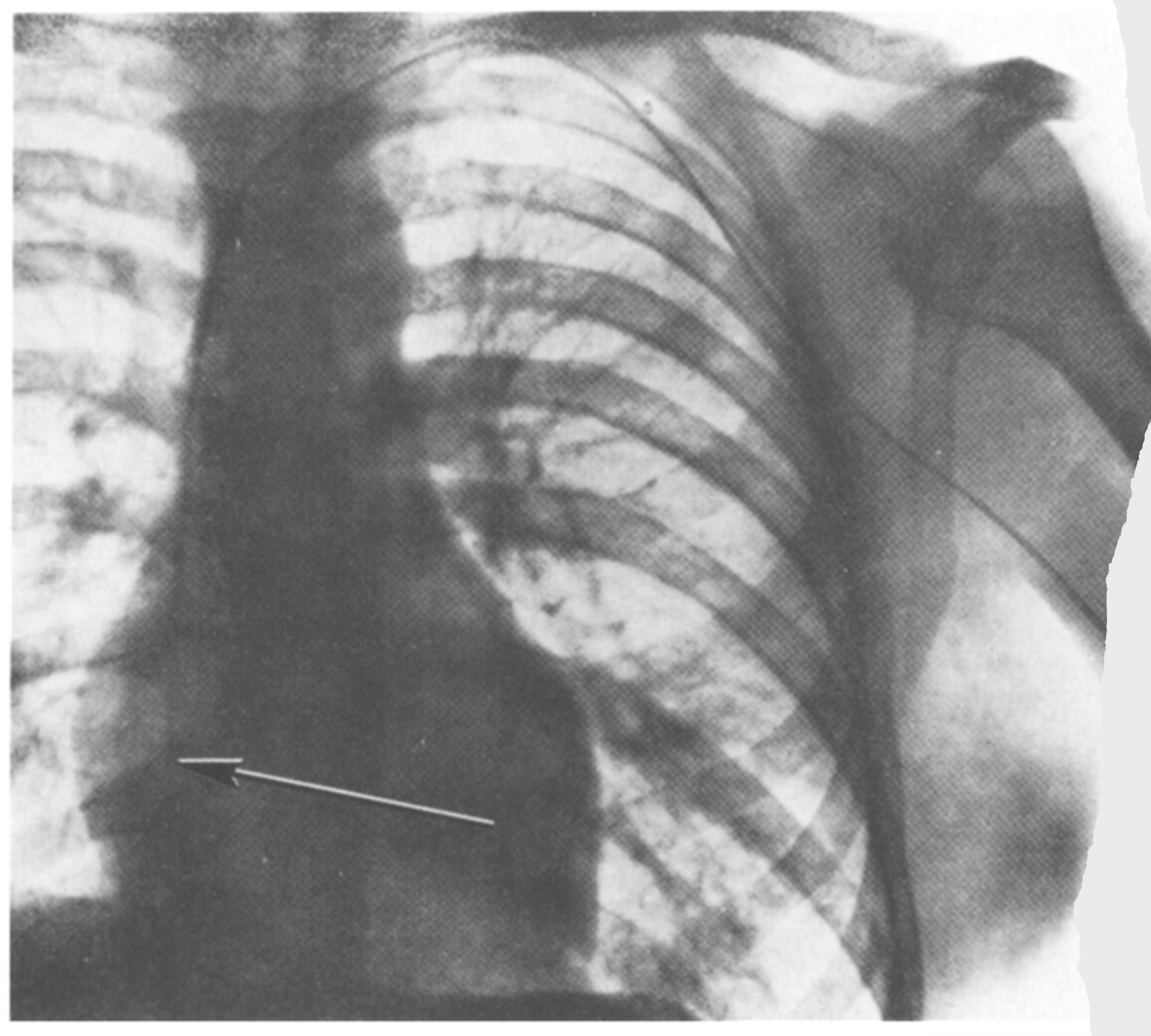
# The Morbid Anatomy Era: PH Was Diagnosed on the Autopsy Table

## DIAGNOSIS FOUND AT AUTOPSY

### AUTOPSY FINDINGS (GROUP 1 PAH)

1891 PULMONARY VASCULAR  
SCLEROSIS -  
Diagnosis Confirmed  
Post-Mortem.  
Total occlusion of vessels,  
RV Failure.

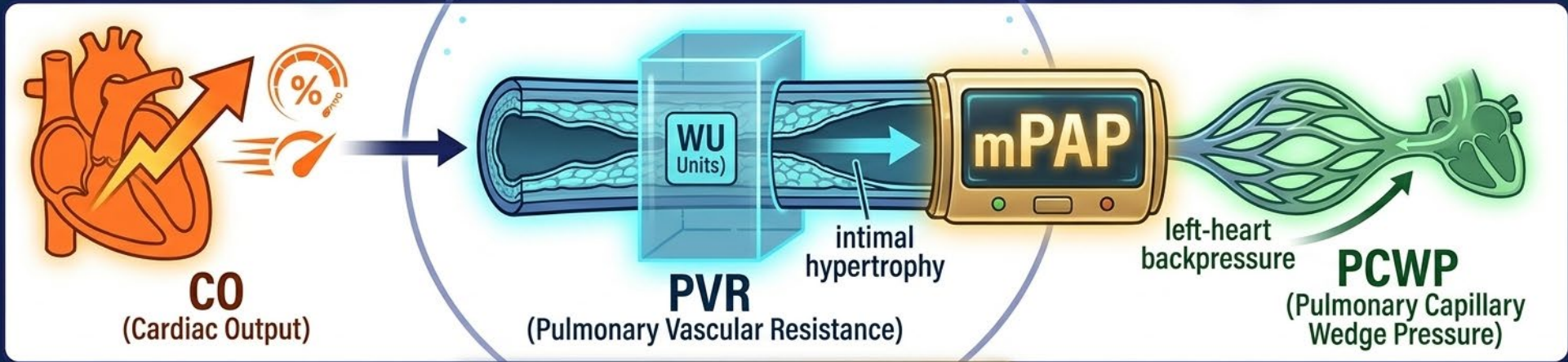




Werner  
Forssmann  
(1929)

# Hemodynamic Equation

$$mPAP = (CO * PVR) + PCWP$$



The Hemodynamic Foundation

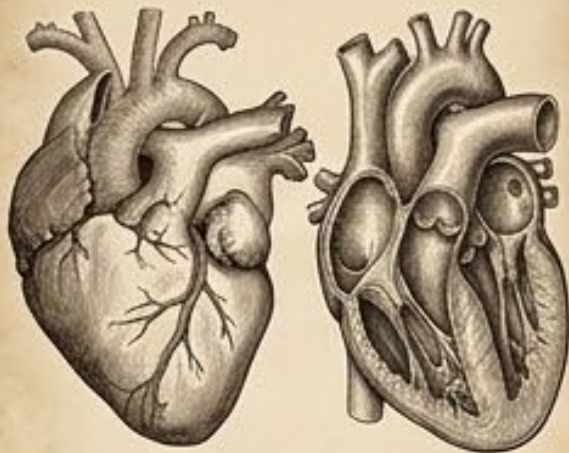
Measurement	Normal Value
mPAP	10–20 mmHg
PVR	0.5–2.0 Wood Units
PCWP	4–12 mmHg
CO	4–6 L/min
RAP	2–6 mmHg

# No Viable Treatment Options...

...But at least it's rare

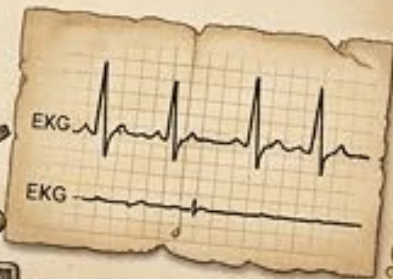
1891-1950s

# THE MORBID ANATOMY ERA.



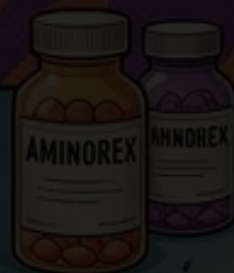
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1980s-1990s

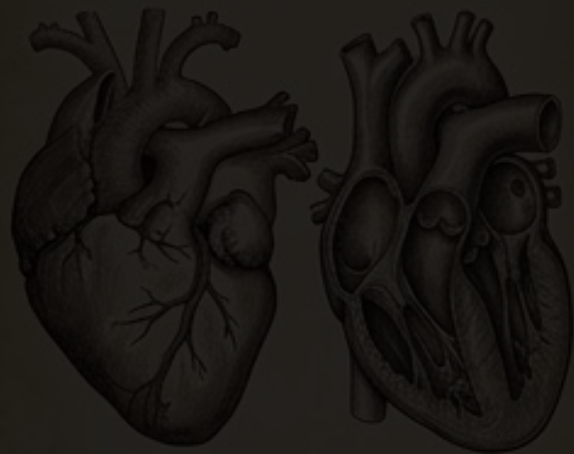
# THE NATURAL HISTORY ERA.

NIH REGIS

Median Sur  
without trea  
~2.8 yea

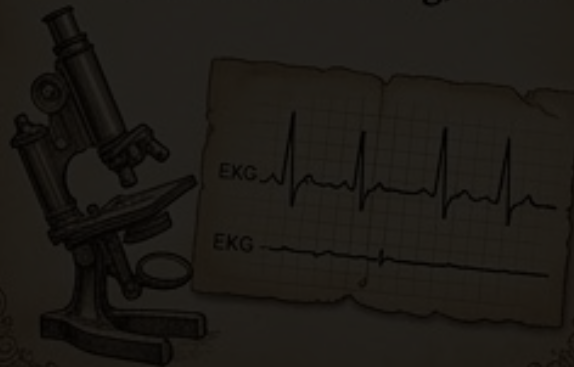


1891-1950s  
**THE MORBID ANATOMY ERA.**

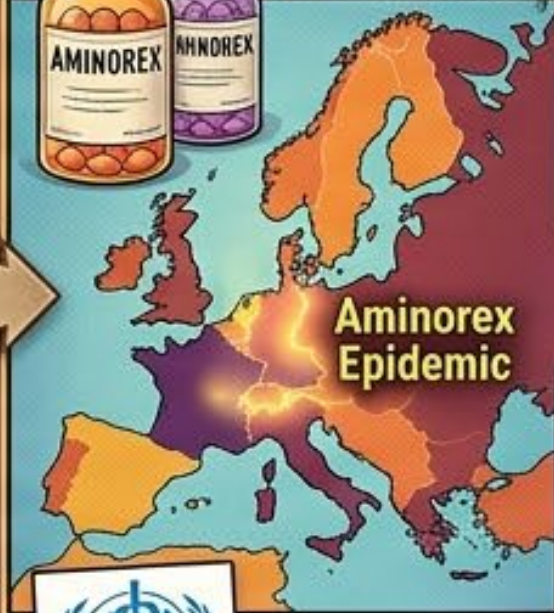


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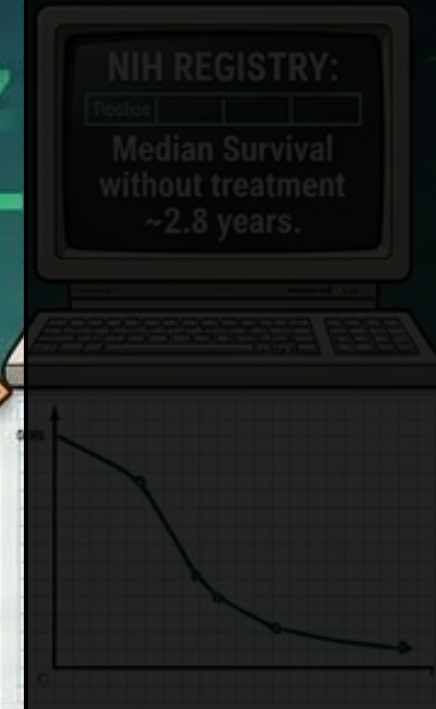
1960s  
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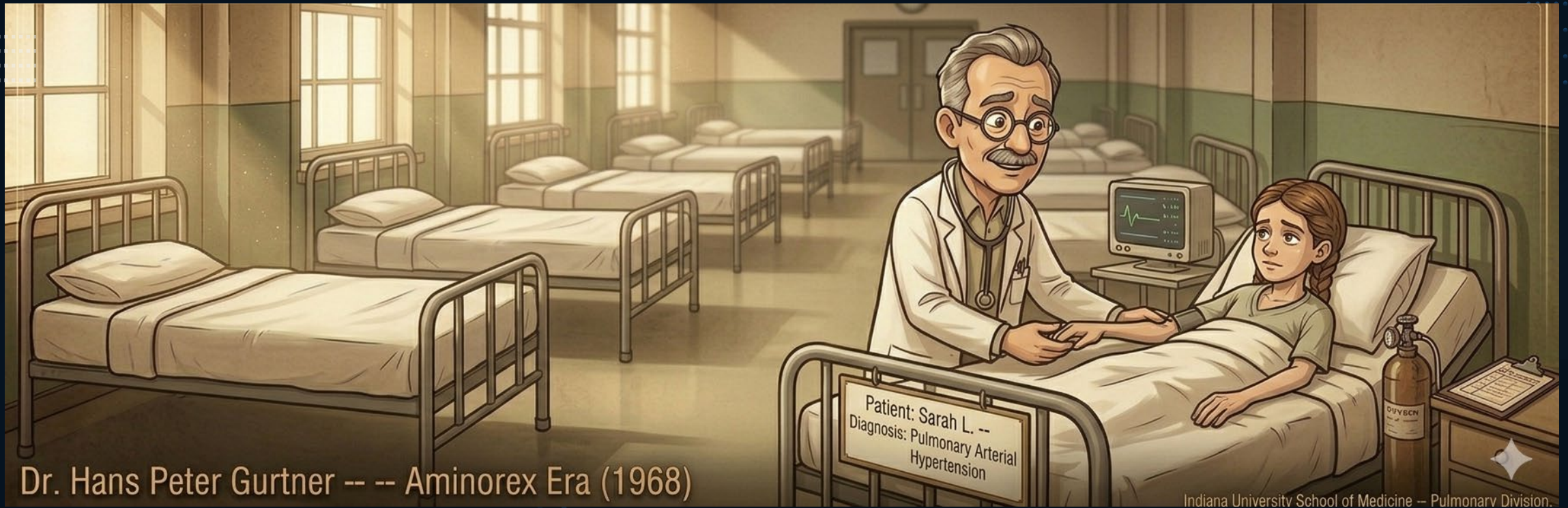


1980s-1990s  
**THE NATURAL HISTORY ERA.**



1990s  
**THE ICE PAC ERA.**



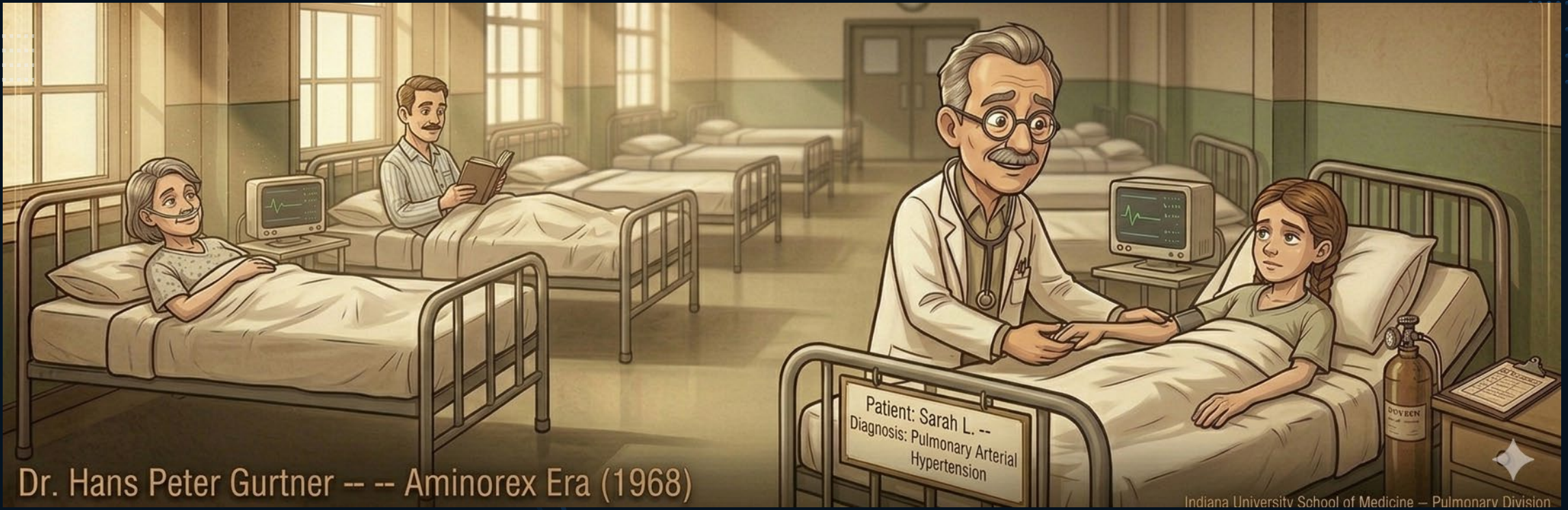


Dr. Hans Peter Gurtner -- -- Aminorex Era (1968)

Indiana University School of Medicine -- Pulmonary Division.

# The Epidemic

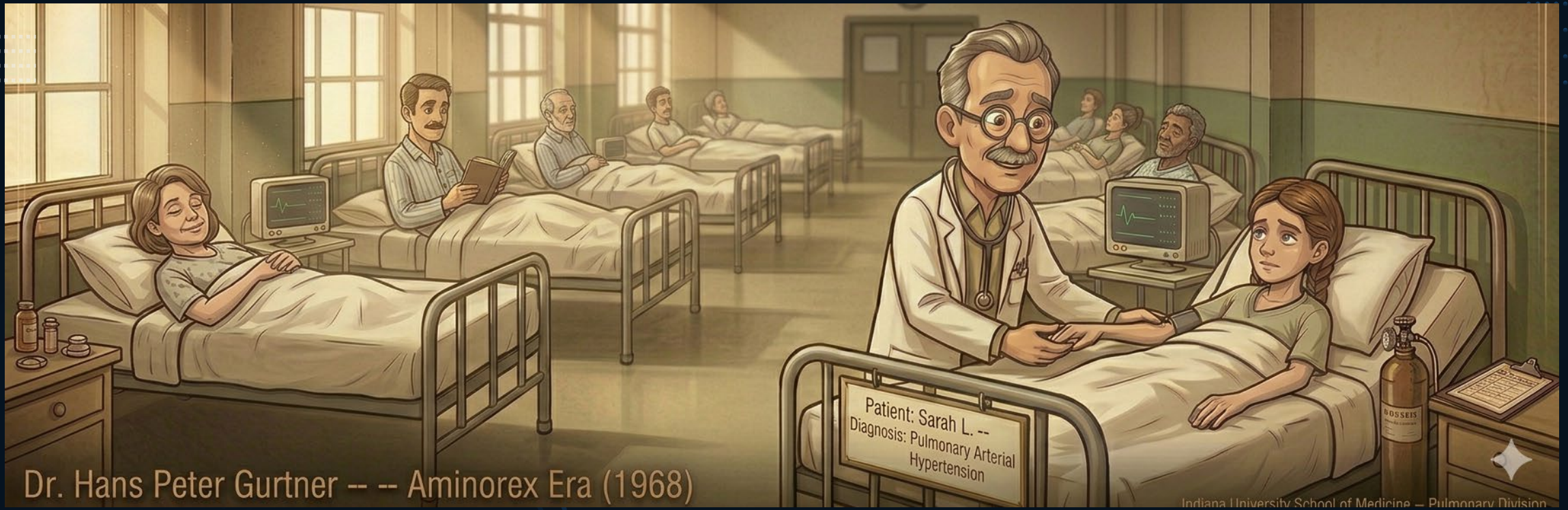
20-fold increase



Dr. Hans Peter Gurtner -- -- Aminorex Era (1968)

Indiana University School of Medicine – Pulmonary Division

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Dr. Hans Peter Gurtner -- -- Aminorex Era (1968)

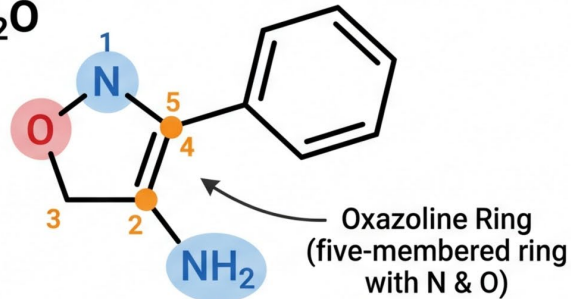
Indiana University School of Medicine -- Pulmonary Division

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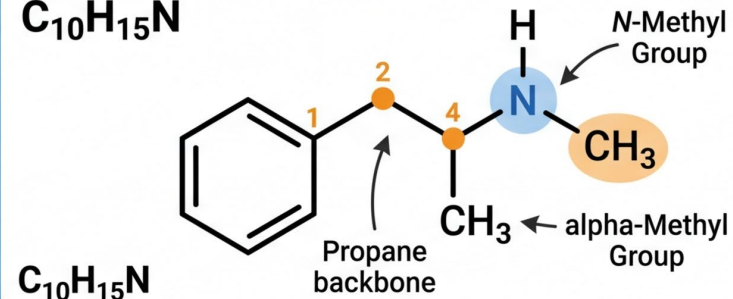
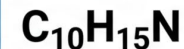
# Drug Associated Pulmonary Hypertension

## CHEMICAL STRUCTURES OF AMINOREX, METHAMPHETAMINE, AND FENFLURAMINE

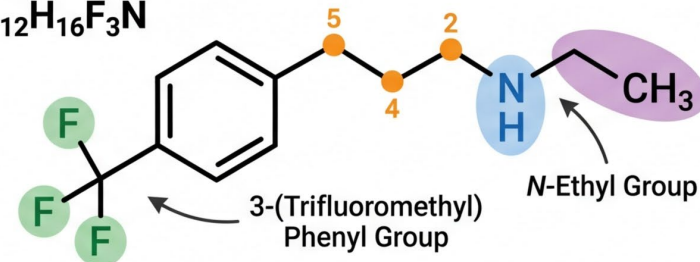
### 1. AMINOREX



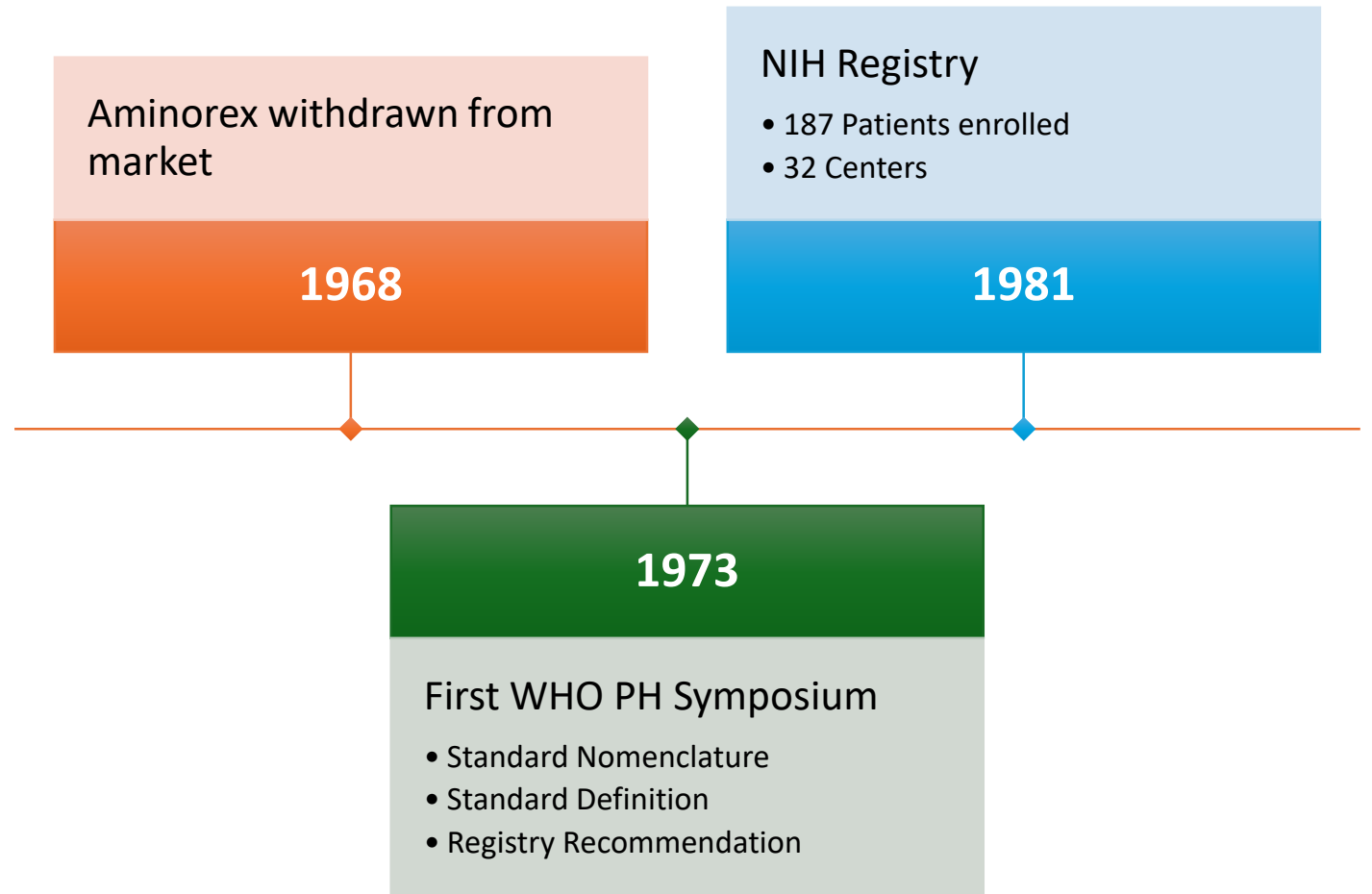
### 2. METHAMPHETAMINE



### 3. FENFLURAMINE



# Aminorex Implications



# WHO Symposium Definitions

Definition

• n  
• P  
The definition of  $\geq 25$  mmHg  
remained the definition for 45  
years

Classification

- P
- Secondary
- Associated.

Aminorex withdrawn from market

1968

NIH Registry

- 187 Patients enrolled
- 32 Centers

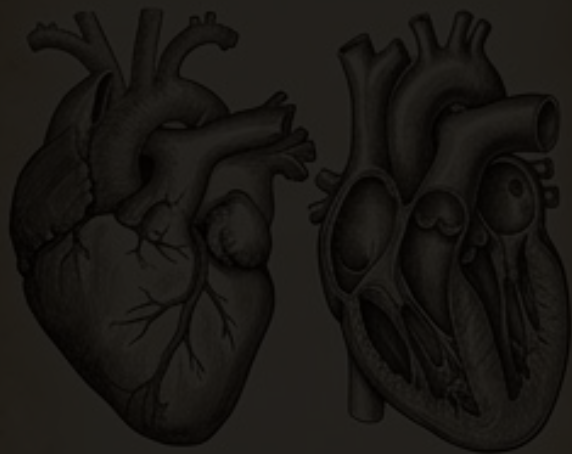
1981

1973

First WHO PH Symposium

- Standard Nomenclature
- Standard Definition
- Registry Recommendation

1891-1950s  
**THE MORBID ANATOMY ERA.**

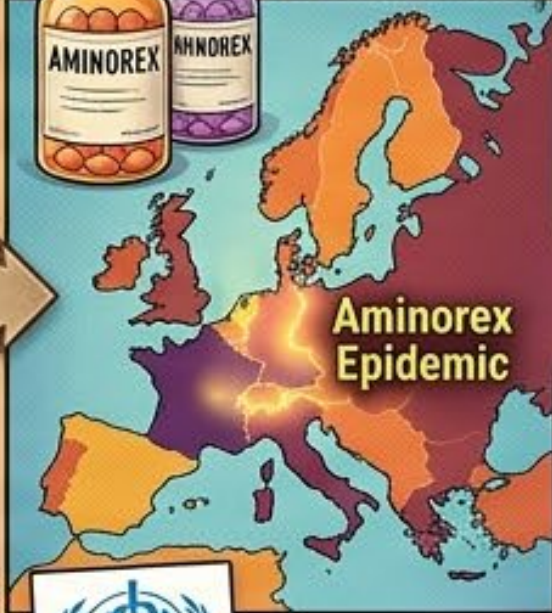


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**THE TOXIC TRIGGER ERA.**



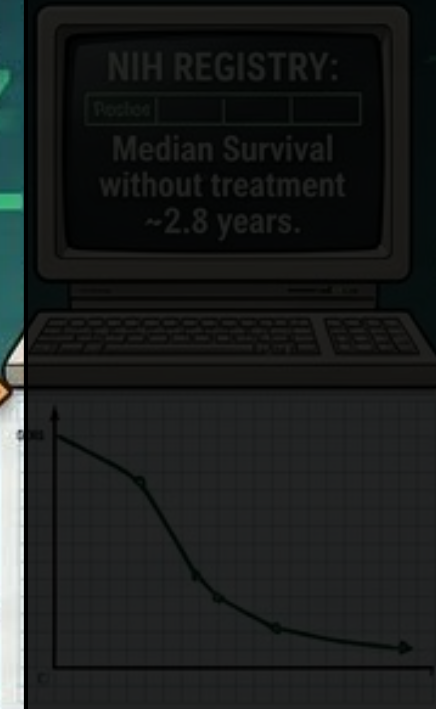
**Aminorex Epidemic**



**1st WHO PH Symposium (1973)**



1980s-1990s  
**THE NATURAL HISTORY ERA.**



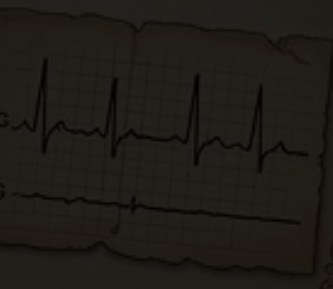
1990s  
**THE ICE PAC ERA.**



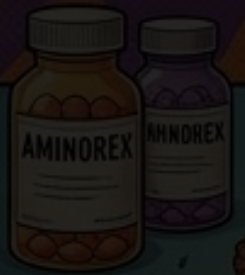
1-1950s  
MORBID  
OMY ERA.



"ventricle was found  
ormous size..."  
on Romberg, 1891



1960s  
THE TOXIC  
TRIGGER ERA.



Aminorex  
Epidemic



1st WHO PH  
Symposium (1973)



1980s-1990s  
THE NATURAL  
HISTORY ERA.



NIH REGISTRY:  
Prostos  
Median Survival  
without treatment  
~2.8 years.



1990s  
THE  
ICE PACK  
ERA.



'cold chain' logistics chain

IV EPOPROSTENOL



1995 FDA Approval

2000s-early 2010s  
THE  
TABLET  
ERA.



ERA  
(AMBRISENTAN)

PDE5  
(SILDENAFIL)

3-strata risk assessment

High	High
2nd	Coctrial
Low	3-strata

Sequential  
monotherapy

VS.

Upfront  
combo therapy

# NIH Registry Findings

## Mean age

- 36 years

## Female : male

- 1.7

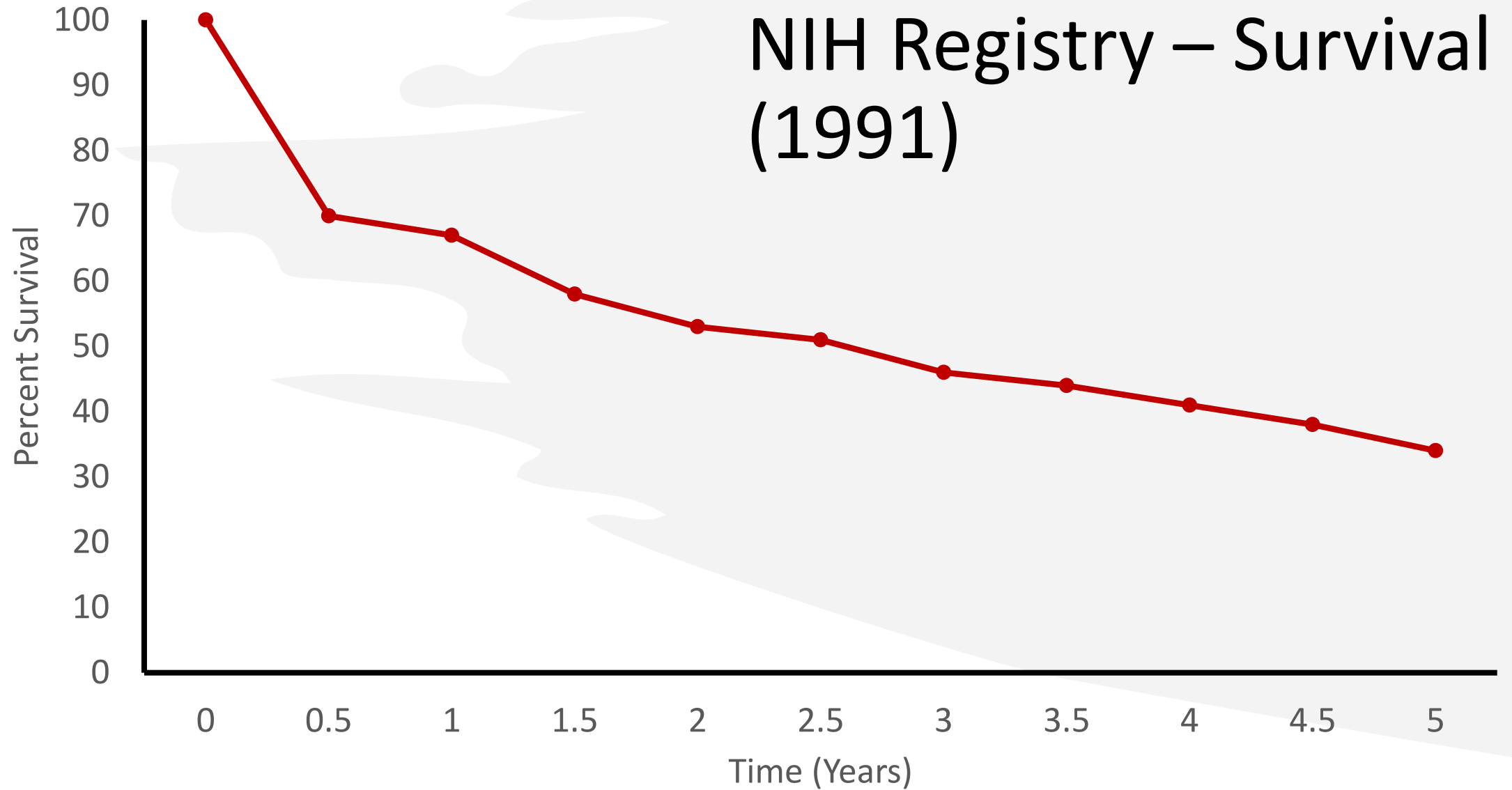
## Average 2-year delay to time of diagnosis

- mPAP was 60 mmHg at time of diagnosis

## Prognostic variables

- NYHA III and IV
- Elevated RA pressure
- Elevated mPAP
- Decreased cardiac index
- Decreased DLCO

# NIH Registry – Survival (1991)



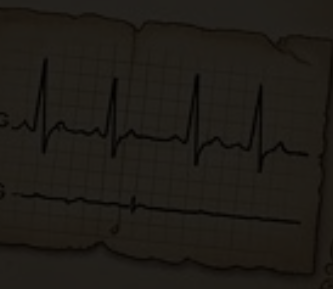
# Medications Studied

- Isosorbide dinitrate
- Phentolamine
- Hydralazine
- Isoproterenol
- Captopril
- Nifedipine
- Diltiazem
- Prostacyclin PGI<sub>2</sub>

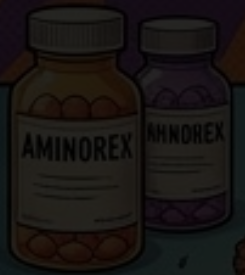
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2000s-early 2010s  
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**AMBITION Trial (2015)**

**Ambrisentan + Tadalafil**

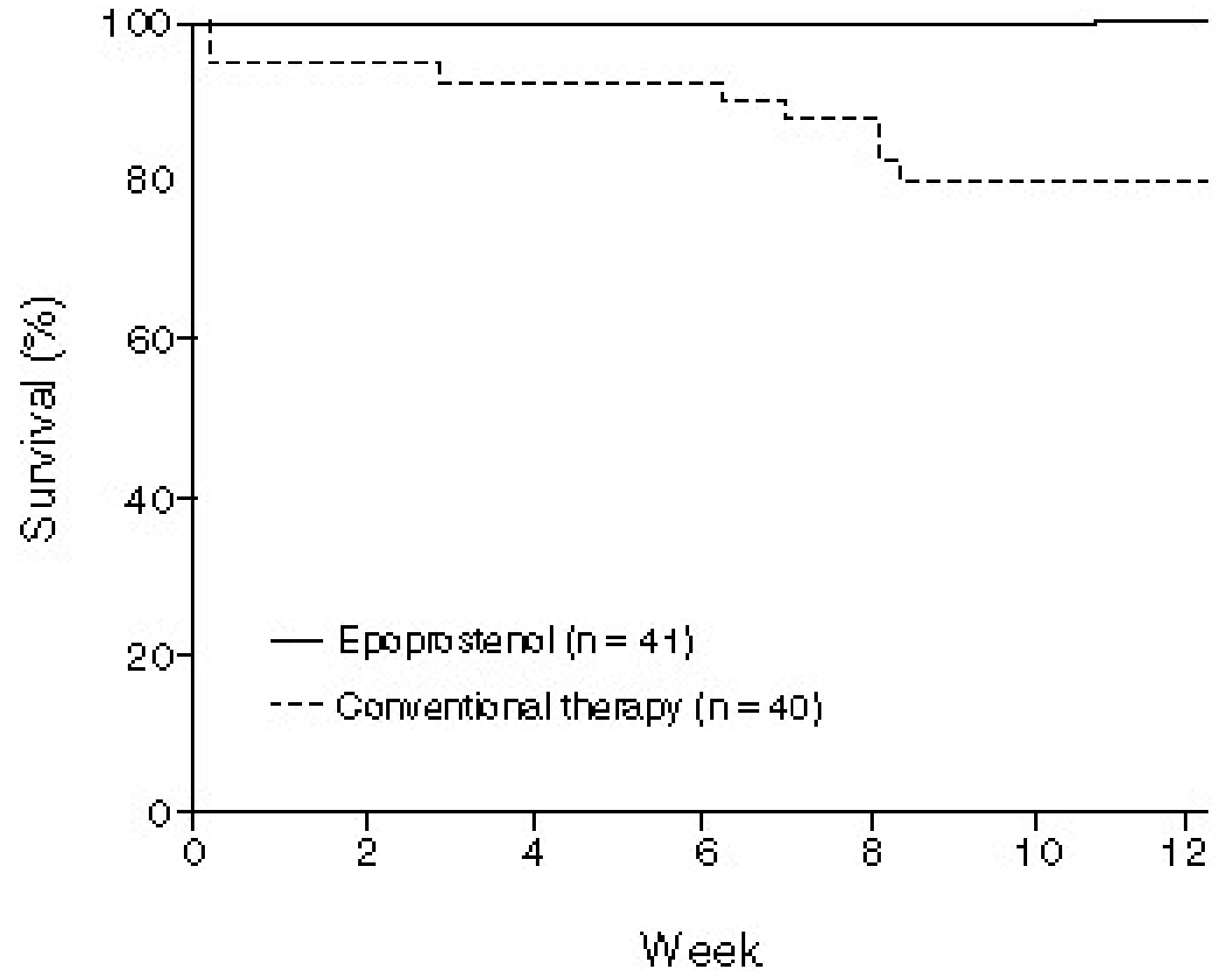
**-5% reduction in clinical events**

**Right Heart-Lung Unit**

**Pills**

# Epoprostenol – 1995

---



# HIGHLIGHTS FROM THE 1996 EPOPROSTENOL TRIAL

LANDMARK 12-WEEK RANDOMIZED CONTROLLED STUDY (PPH PATIENTS) 1967-Modern



## IMPROVED SURVIVAL

- 100% (41/41) epoprostenol
- 80% (32/40) conventional
- First cileuiniicatus of  $\alpha$  1- $\hat{c}$



## 6-MINUTE WALK TEST (6MWT)

- +47m epoprostenol  $P < 0.01$
- -66m conventional,  $P < 0.01$



## HEMODYNAMIC BASIS



- mPAP Reduction
- PVR Reduction



## FUNCTIONAL STATUS & QOL

- At least 1 NYHA Functional Class improvement for  $> 50\%$
- Improved Quality of Life (QoL) Scores (Dyspnea, Fatigue)

## COLUMN LEGEND

 **EPOPROSTENOL GROUP (FLOLAN)** 

 **CONVENTIONAL THERAPY (CONTROL)**



KEY TAKEAWAY: First pharmacological therapy to prove reduced mortality in PAH. Divergence from Historical 2.8-Year Median



**INDIANA UNIVERSITY**  
School of Medicine - Pulmonary Division.



That Sounds Great!!

# CONS OF THE ORIGINAL EPOPROSTENOL FORMULATION

A LOGISTICAL CHALLENGE FOR PATIENTS (PRE-THERMOSTABLE ERA)



## LOGISTICAL CONS



**NEED FOR FANNY PACK**  
(ICE PACK CHANGE < 8 HRS)



**SHORT HALF-LIFE**  
(< 6 MINUTES in bloodstream)

Constant cooling requirement



## INFECTION & LINE MANAGEMENT

**CATHETER-RELATED INFECTION (CRI)**, venous thrombosis.

Need for consistent sterile technique.

## HEMODYNAMIC CONSEQUENCES



- Extreme sensitivity to dose titration, risk of rebound pulmonary hypertension upon sudden discontinuation.
- High PVR with unstable delivery.

## SYSTEMIC SIDE EFFECTS



**SYSTEMIC EFFECTS**

Vasodilation-mediated  
(Flushing, Nausea)



## CONS LEGEND



**ICE PACK REQUIREMENT**



**CADD PUMP**



**INFECTION RISK**



**INFECTION RISK**



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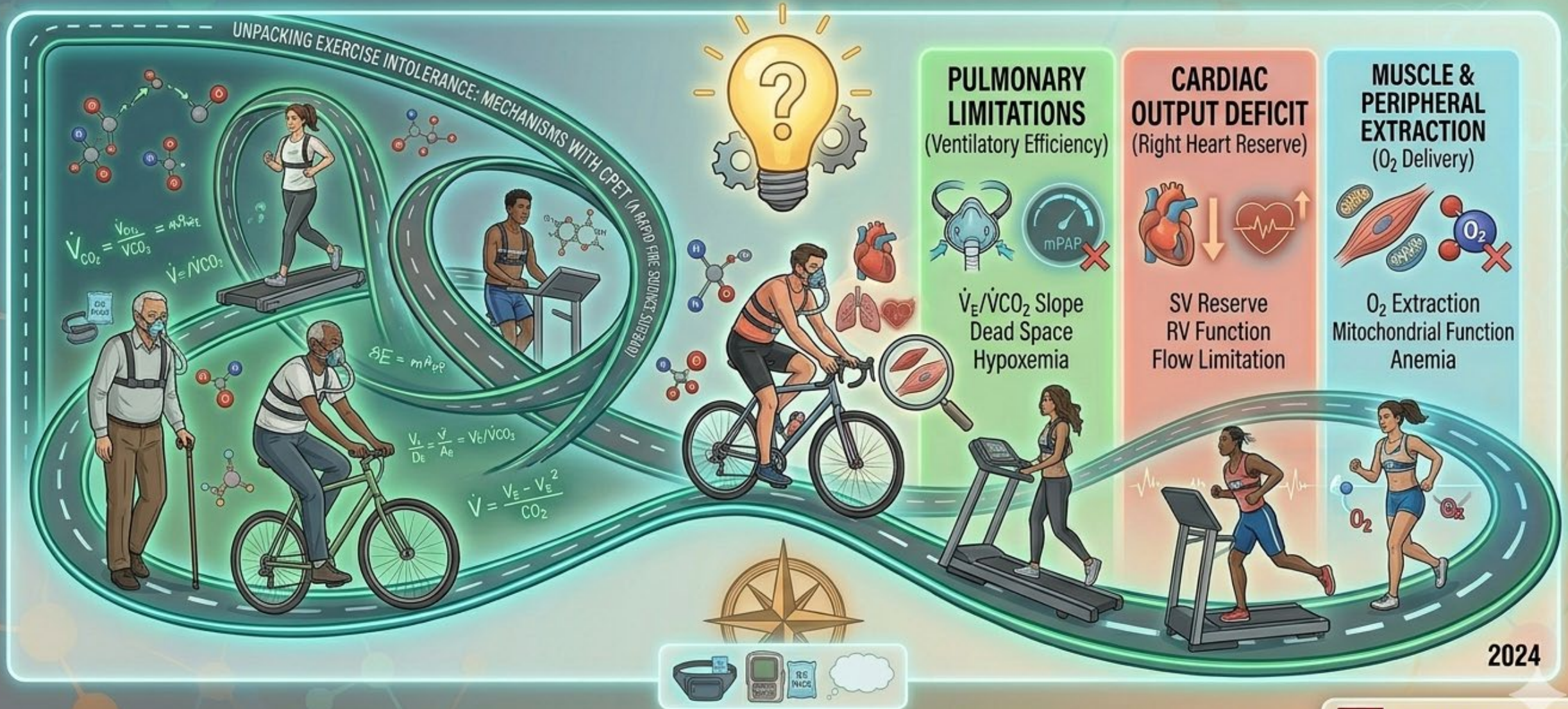
Right Heart-Lung Unit

Right Heart-Lung Unit

Pills

# AND NOW... A DETOUR INTO DATA! (GET READY TO GO FASTER!)

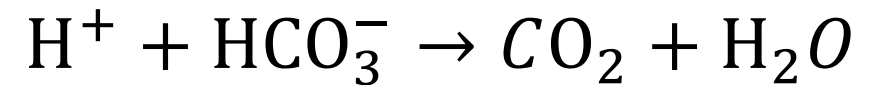
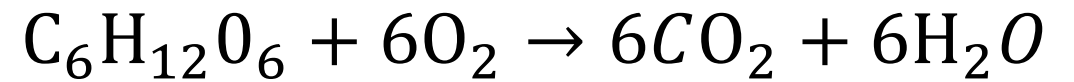
UNPACKING EXERCISE INTOLERANCE: MECHANISMS WITH CPET (A RAPID-FIRE SCIENCE SIDEBAR)



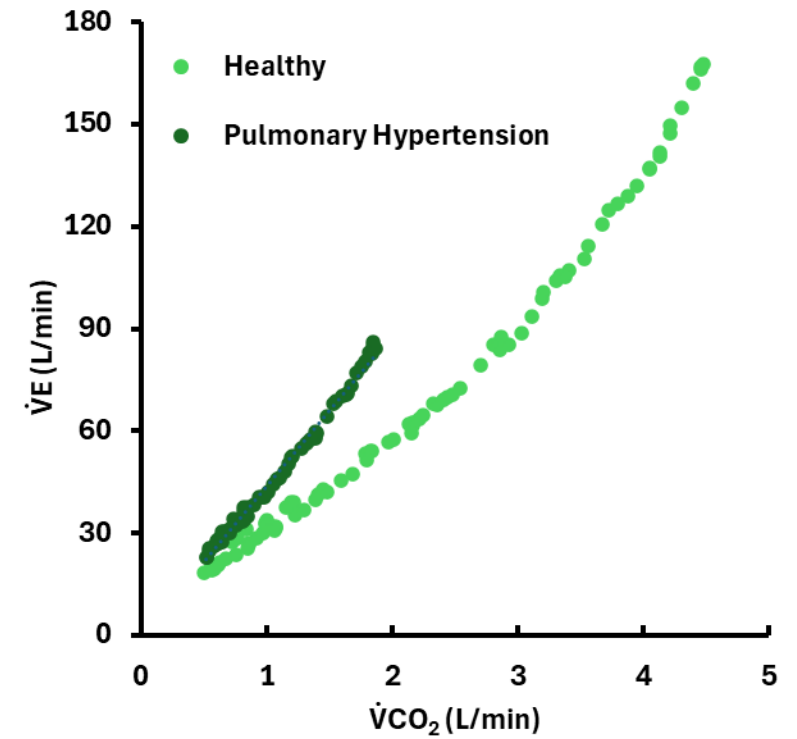
KEY TAKEAWAY: First pharmacological therapy to prove reduced mortality in PAH. Reduced Pressure, Better Function

# Mechanisms of Exercise Intolerance

$$\dot{V}O_2 = \dot{Q} \cdot (C_{aO_2} - C\bar{v}O_2)$$

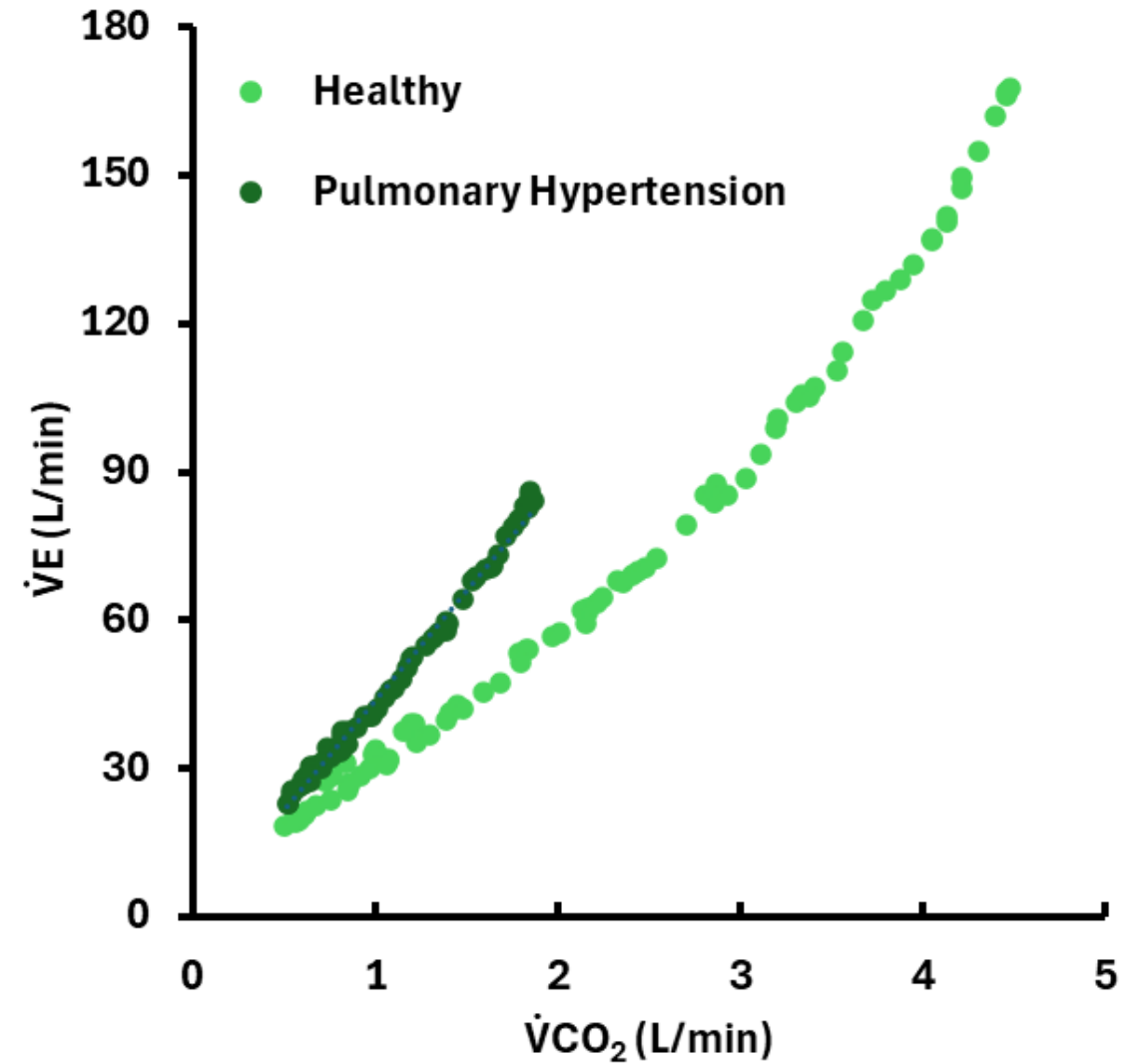
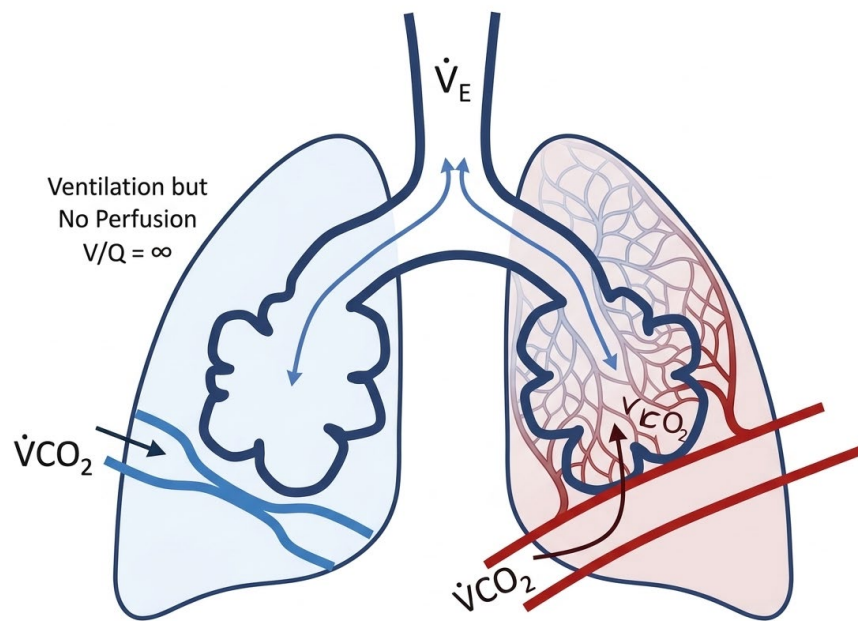


# Mechanisms of Exercise Intolerance



# Ventilatory Inefficiency

$$\frac{\dot{V}_E}{\dot{V}_{CO_2}} = \frac{863}{P_aCO_2 \cdot \left(1 - \frac{V_D}{V_T}\right)}$$



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ERA  
(AMBRISENTAN)

PDE5-I  
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2nd	Cochinal
Low	3-strata

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Nebulizer

# 2020s and beyond THE MOLECULAR ERA.

Targeted

Advanced 4-strata

Low	Inter-Low	Inter-High
Low	Inter-Low	Inter-High
Low	Inter-Low	Inter-High
High	High	High

GREEN ZONE

Personalized Medi

Genomic data

Cu

# The First Wave

## 2001 – BREATHE-1 Trial

- Boesntan -- ERA
- 1° Outcome – 6 min walk test
  - Placebo - 8 meters
  - Low dose + 27 meters
  - High dose + 54 meters
- 2° Outcome
  - Improved FC
  - Improved dyspnea scores
- Safety
  - Hepatic toxicity (10%)
  - Teratogenicity



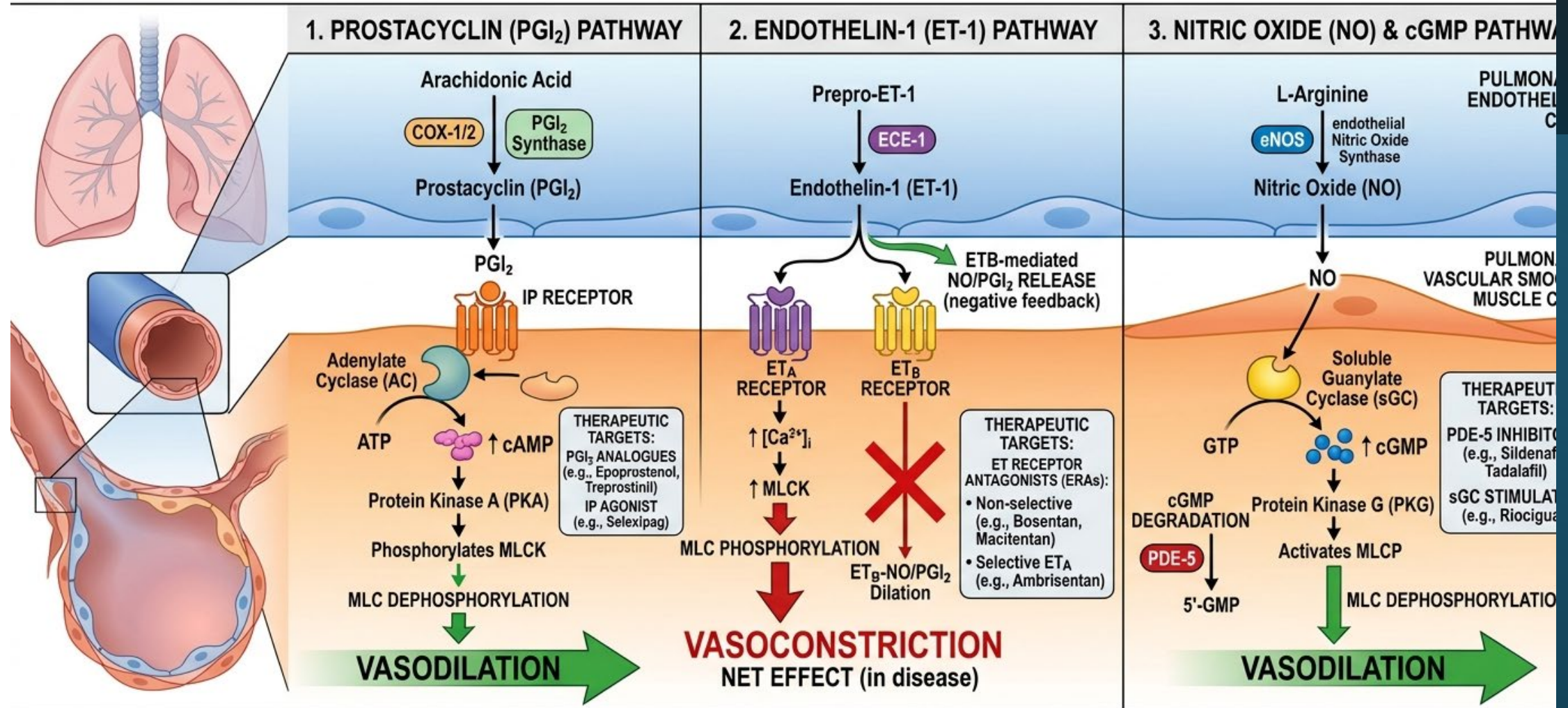
# The First Wave



## 20025– SUPER-1 Trial

- 1° Outcome – 6 min walk test
  - Improved 45-50 meters all doses
- 2° Outcome
  - Significant reduction in mPAP and PVR
  - Improved dyspnea scores
- Safety
  - Mild side effects

# THREE BASIC PULMONARY VASODILATOR MECHANISMS



FINAL EFFECT ON PULMONARY VASCULAR RESISTANCE (PVR):

→ ↓ PVR **VASODILATION**

# Summary of PH Pharmaceuticals

PGI<sub>2</sub> Path

## **Epoprostenol**

1996

Compared to placebo

Advantages: The first, only drug to reduce mortality

Disadvantages: Stability, half life, side effects, delivery

Pathway

# Summary of PH Pharmaceuticals

**PGI<sub>2</sub> Pathway**  
Epoprosterol

## **Bosentan – BREATHE-1**

2002 (oral)

Compared to placebo

Advantages: Oral

Disadvantages: Liver toxicity, teratogenicity

**Pathway**

# Summary of PH Pharmaceuticals

**PGI<sub>2</sub> Pathway**  
Epoprostenol

## **Treprostinil**

2002 (SC, IV)

Compared to placebo

Advantages: SC modality, chemically stable, SC and IV routes, longer half life

Later: Oral and inhaled formulations

**Pathway**

# Summary of PH Pharmaceuticals

**PGI<sub>2</sub> Path**

Epoprostenol

Treprostinil

## **Iloprost – AIR Trial**

2002 (inhaled)

Compared to placebo

Advantages: No central lines!

Disadvantages: 6-9 times daily

No Longer Available

**Pathway**

# Summary of PH Pharmaceuticals

**PGI<sub>2</sub> Pathway**

1996 – Epoprostenol

Treprostinil

Iloprost

## **Sildenafil / SUPER-1 Trial**

2005

Compared to placebo

Advantages: Safe, oral

**Pathway**

# Summary of PH Pharmaceuticals

**PGI<sub>2</sub> Pathway**

Epoprosterol

Treprostinil

Iloprost

## **Ambrisentan – ARIES-1 / -2**

2008 (oral)

Compared to placebo

Advantages: Oral, less liver toxicity, selective

Disadvantages: Teratogenicity

**Pathway**

# Summary of PH Pharmaceuticals

**PGI<sub>2</sub> Pathway**

Epoprosterol

Treprostinil

Iloprost

## **Tadalafil / PHIRST Trial**

2009

Compared to placebo (but half on bosentan)

Advantages: Once daily

**Pathway**

# Summary of PH Pharmaceuticals

PGI<sub>2</sub> Pathway

Epoprostenol

Treprostinil

Iloprost

## Riociguat / PATENT-1 Trial

2013

Compared to placebo (half were on background)

Advantages: Approved for CTEPH, more potent

Note: **CANNOT COMBINE WITH PDE5i**

Pathway

# Summary of PH Pharmaceuticals

**PGI<sub>2</sub> Pat**

Epoprostenol

Treprostinil

Iloprost

## **Macitentan – SERAPHIN**

2013 (oral)

Compared to placebo / background

Advantages: Oral, less liver toxicity, better tissue penetration

Disadvantages: Teratogenicity

**Pathway**

# Summary of PH Pharmaceuticals

**PGI<sub>2</sub> Pathway**

Epoprostenol

Treprostinil

Iloprost

## **Selexipag – GRIPHON**

2015 (oral)

Compared to background

Advantages: Oral, no proprietary pumps, inhalers

**Pathway**

# Summary of PH Pharmaceuticals

## **PGI<sub>2</sub> Pathway**

Epoprostenol  
Treprostinil  
Iloprost  
Selexipag

## **Endothelin Pathway**

Bosentan  
Ambrisentan  
Macitentan

## **Nitric Oxide Pathway**

Sildenafil  
Tadalafil  
Riociguat

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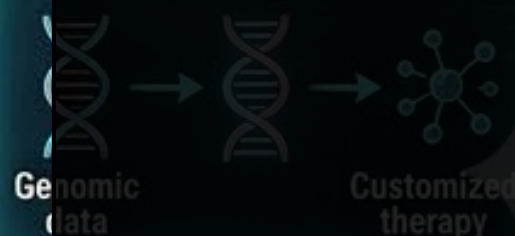


Targeted receptor

Advanced 4-strata

Low	Inter-Low	Inter-High	High
Low	Inter-Low model	GREEN ZONE	
High			

Personalized Medicine



Genomic  
data

Customized  
therapy

# We have the tools...

Now how do we use them?



# Redefined Hemodynamic Thresholds



**MPAP > 20 mmHg**

Previously  $\geq 25$  mmHg



**PVR >2**

Previously > 3



**PCWP  $\leq 15$  mmHg**

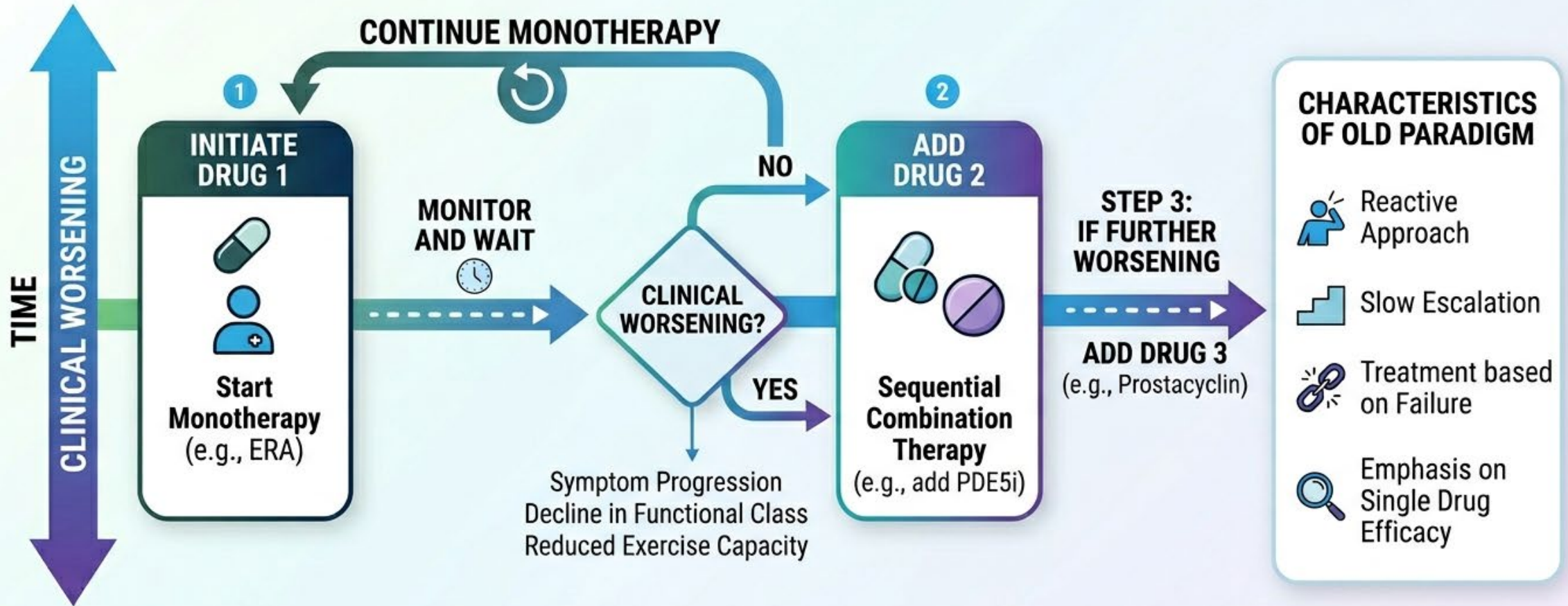
# Pulmonary Hypertension Severity

$$MPAP = CO \cdot PVR + PCWP$$

# Pulmonary Hypertension Severity

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
WHO-FC	I, II	III	IV
6MWD <sup>c</sup>	>440 m	165–440 m	<165 m
CPET	Peak VO <sub>2</sub> >15 mL/min/kg (>65% pred.) VE/VCO <sub>2</sub> slope <36	Peak VO <sub>2</sub> 11–15 mL/min/kg (35–65% pred.) VE/VCO <sub>2</sub> slope 36–44	Peak VO <sub>2</sub> <11 mL/min/kg (<35% pred.) VE/VCO <sub>2</sub> slope >44
Biomarkers: BNP or NT-proBNP <sup>d</sup>	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm <sup>2</sup> TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm <sup>2</sup> TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm <sup>2</sup> TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI <sup>e</sup>	RVEF >54% SVI >40 mL/m <sup>2</sup> RVESVI <42 mL/m <sup>2</sup>	RVEF 37–54% SVI 26–40 mL/m <sup>2</sup> RVESVI 42–54 mL/m <sup>2</sup>	RVEF <37% SVI <26 mL/m <sup>2</sup> RVESVI >54 mL/m <sup>2</sup>
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m <sup>2</sup> SVI >38 mL/m <sup>2</sup> SvO <sub>2</sub> >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m <sup>2</sup> SVI 31–38 mL/m <sup>2</sup> SvO <sub>2</sub> 60–65%	RAP >14 mmHg CI <2.0 L/min/m <sup>2</sup> SVI <31 mL/m <sup>2</sup> SvO <sub>2</sub> <60%

# OLD PARADIGM: SEQUENTIAL MONOTHERAPY IN PAH



# SUMMARY OF KEY PAH COMBINATION THERAPY TRIALS: LANDMARK DATA

## SERAPHIN (2013)<sup>[3]</sup>

### ADDING MACITENTAN TO BACKGROUND THERAPY



- **Population:** 742 Symptomatic PAH (WHO FC II-IV)
- **Intervention:** Macitentan (10 mg or 3 mg) vs. Placebo on Background Therapy (64% PDE5i)<sup>[1-7]</sup>
- **PRIMARY ENDPOINT ACHIEVED: 50% RISK REDUCTION IN MORBIDITY/MORTALITY (10% mg, P<0.001)**
- Greater 6MWD Improvement (+49m vs. +24m)
- **CONCLUSION:** Upfront Dual Therapy is superior to Sequential Monotherapy, changing the paradigm.

## GRIPHON (2015)<sup>[6]</sup>

### ADDING SELEXIPAG TO VARIED BACKGROUNDS



- **Population:** 1,156 Symptomatic PAH (20% Naive, 80% Background)<sup>[1-6]</sup>
- **Intervention:** Selexipag (titrated) vs. Placebo
- **PRIMARY ENDPOINT ACHIEVED: 40% RISK REDUCTION IN MORBIDITY/MORTALITY (P<0.001)**
- Consistent Benefit across all subgroups (Naive, Mono, Doal Background)
- **CONCLUSION:** Demonstrated clear long-term benefit of adding macitentan to existing therapy.

## AMBITION (2015)<sup>[1]</sup>

### UPFRONT DUAL ORAL COMBINATION



- **Population:** 500 Newly Diagnosed, Treatment-Naive (WHO FC II-III)
- **Intervention:** Upfront Ambrisentan + Tadalafil vs. Monotherapy (AMB or TAD)<sup>[1-7]</sup>
- **PRIMARY ENDPOINT ACHIEVED: 50% RISK REDUCTION IN CLINICAL FAILURE (HR 0.50, P<0.001)**
- Greater 6MWD Improvement (+49m vs. +24m)
- **CONCLUSION:** Selexipag is effective when added to monotherapy, dual therapy, or treatment-naïve patients.

## TRITON (2021)<sup>[7]</sup>

### LIMITS OF UPFRONT ORAL TRIPLE THERAPY?



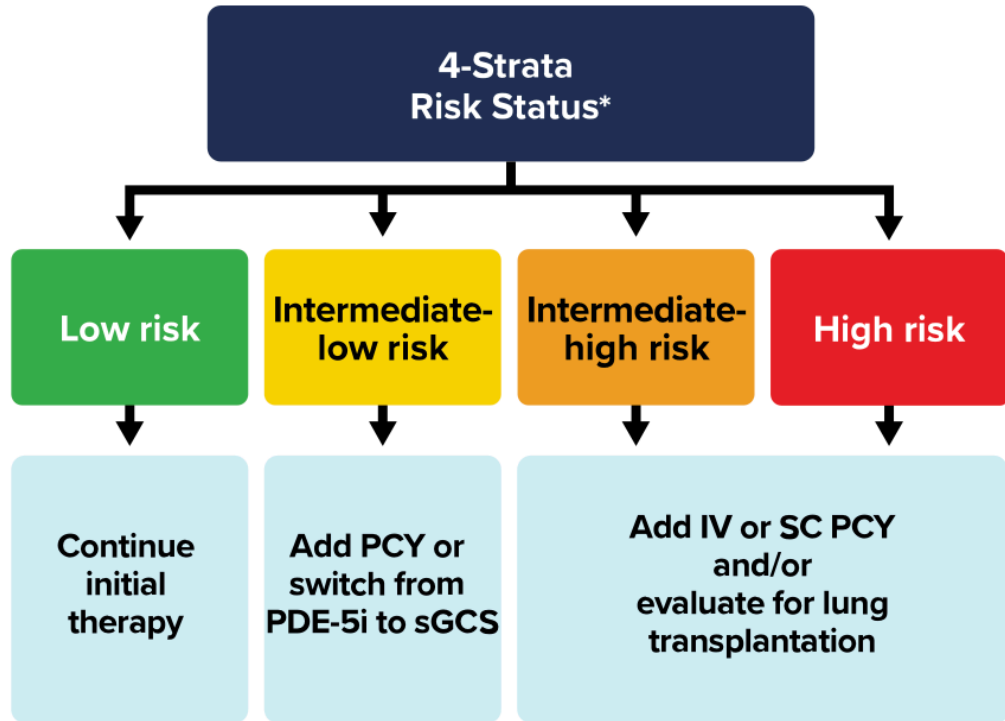
- **Population:** 247 Newly Diagnosed, Treatment-Naïve (WHO FC II-III)<sup>[1-6]</sup>
- **Intervention:** Upfront TRIPLE (Mac+Tad+Sel) vs. Upfront DOUBLE (Mac+Tad)<sup>[7-8]</sup>
- **PRIMARY ENDPOINT NOT MET: NO SIGNIFICANT DIFFERENCE IN PVR REDUCTION AT WEEK 26**
- Both groups showed ~53% PVR reduction
- **CONCLUSION:** Adding a third oral agent upfront didn't provide additional PVR edge over strong dual therapy.

## KEY IMPLICATIONS

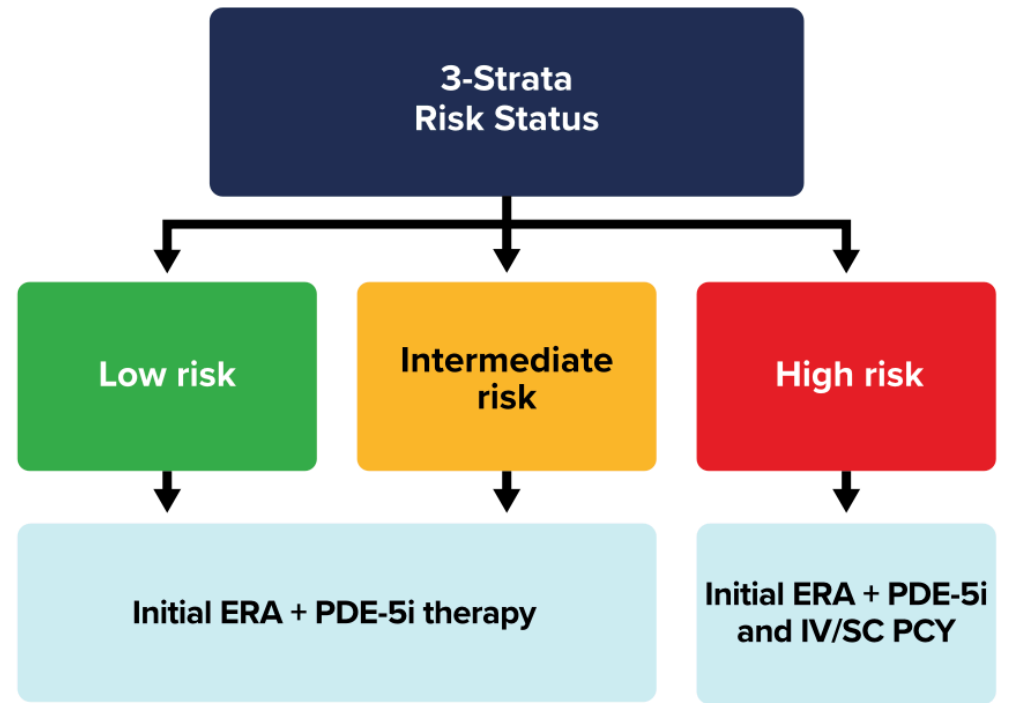
- Sequential Combination (SERAPHIN, GRIPHON) maintains clinical benefit when layered.
- Upfront Dual Oral Therapy (AMBITION) established a new proactive standard.
- The optimal timing for adding a third oral agent upfront (TRITON) remains unclear vs. potent dual therapy.

# Treatment Algorithm

## Follow-Up Treatment Algorithm

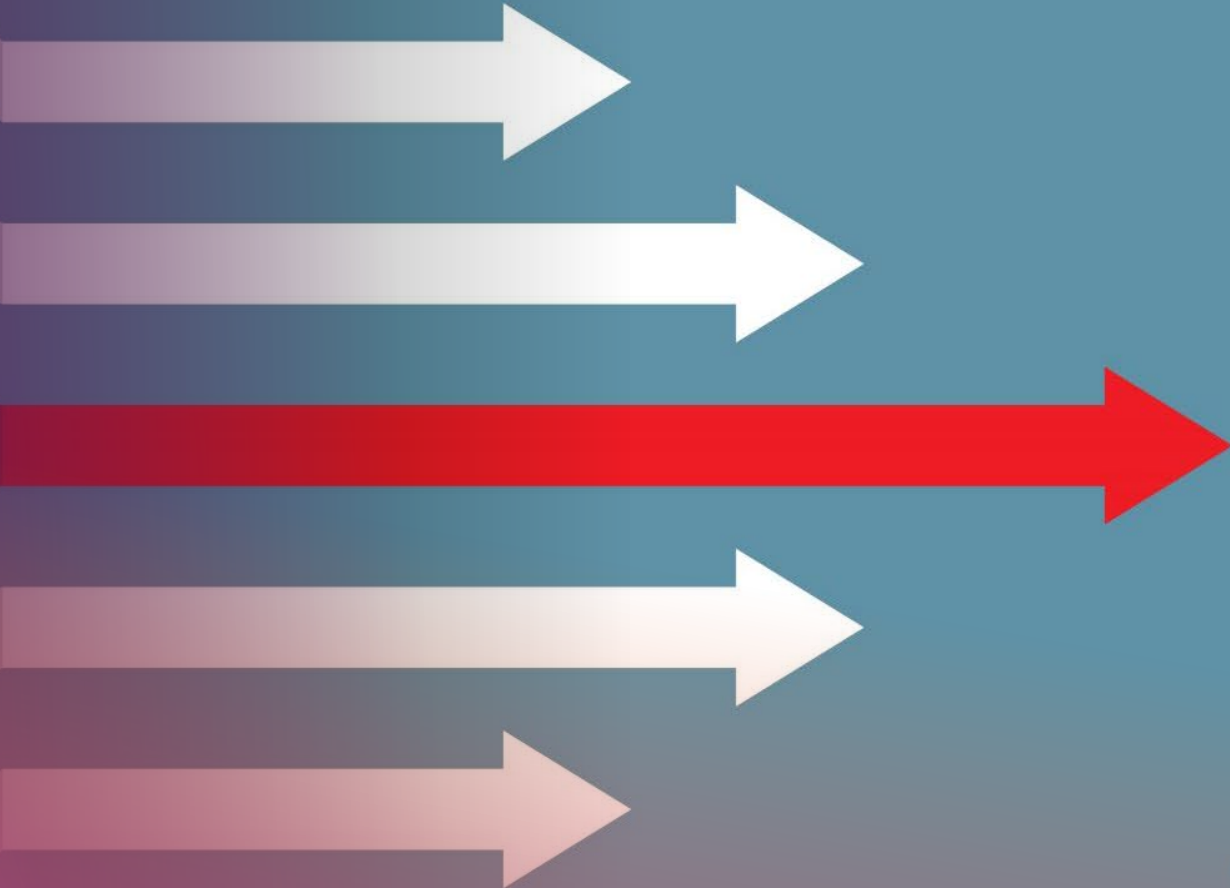


## Initial Treatment Algorithm



Goal

Low Risk



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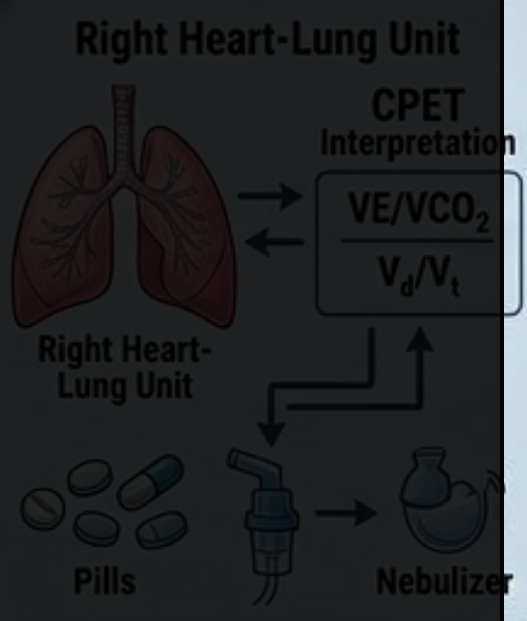
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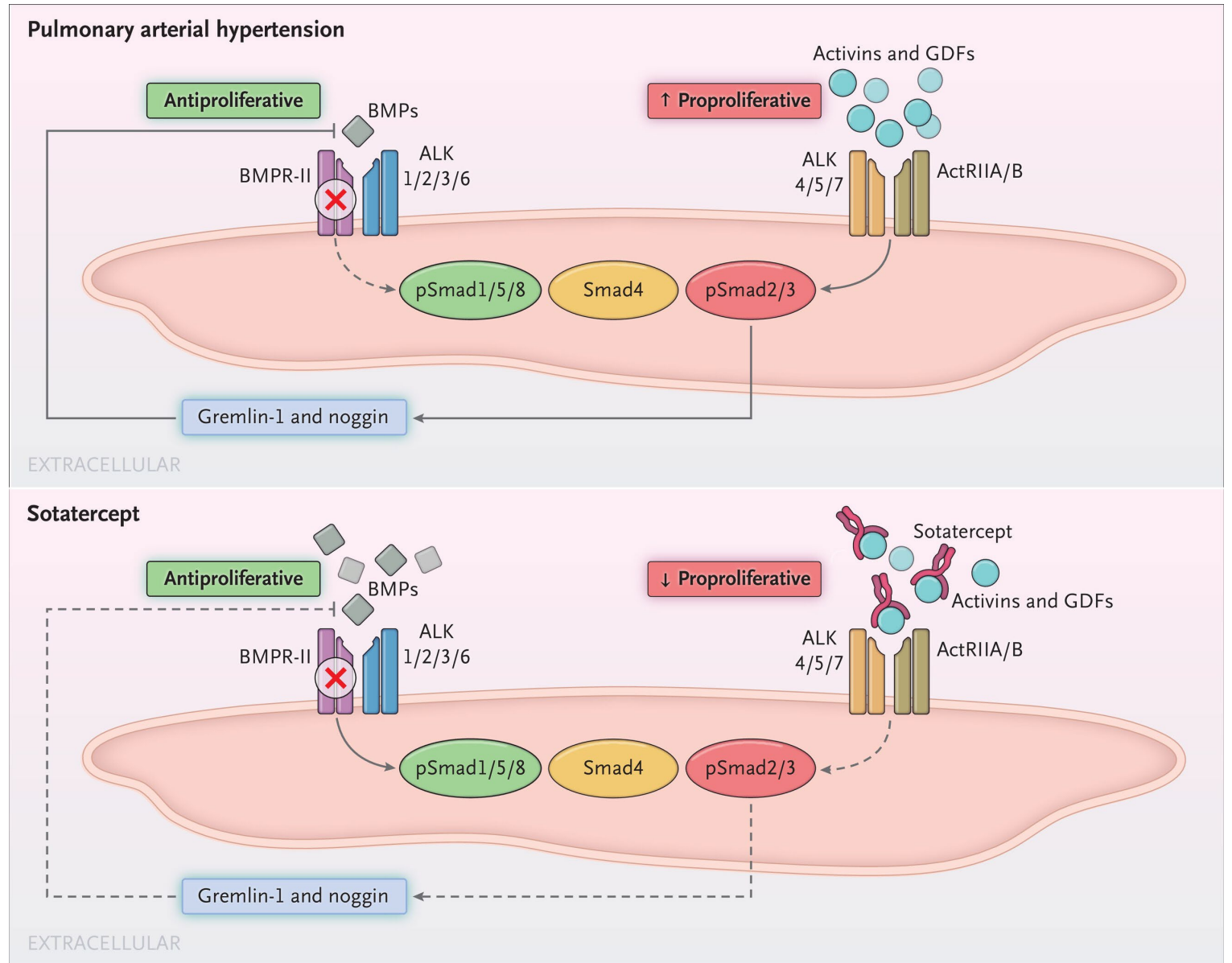


Advanced 4-strata

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Low	Inter-Low model	GREEN ZONE	
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# Sotatercept - - The New Kid on the Block



# The STELLAR Trial

- FC 2-3 PH
- > 60% on triple therapy and 40% on infusions
- Results
  - Improved 6MWD
  - Significant reduction in PVR
  - 84% reduction in clinical worsening or death
- Adverse Events
  - Epistaxis, telangeiectasias, erythrocytosis, thrombocytopenia

# The ZENITH Trial

- Patients – ADVANCED PH
  - FC 3 OR 4
- Results
  - 76% decrease in death, lung transplant, or PH hospitalization
  - NOT walk distance
- Stopped early due to overwhelming efficacy.

# Sotatercept in the Real-World

- Noespleeds
- GI gleeds
- Pericardial effusions
- Intrapulmonary shunts
- Severe erythrocytosis

late 2000s-early 2010s  
**THE TABLET ERA.**



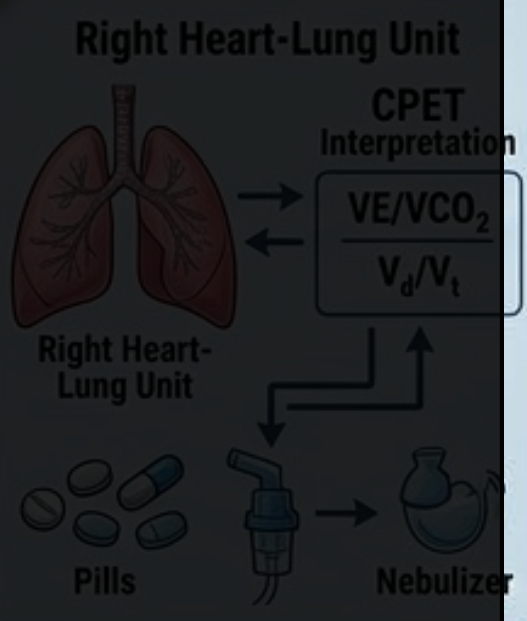
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Low Inter-Low model	<b>GREEN ZONE</b>		
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# Final Thoooughts

