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Updates in Pulmonary Hypertension 2025

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WHO Committees and World Symposia on Pulmonary Hypertension

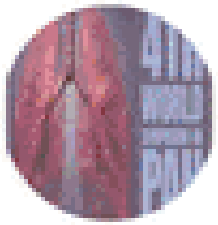
1960 Geneva

1973 Geneva

1998 Evian

2003 Venice

2008 Dana Point



2013 Nice

2018 Nice

2024 Barcelona

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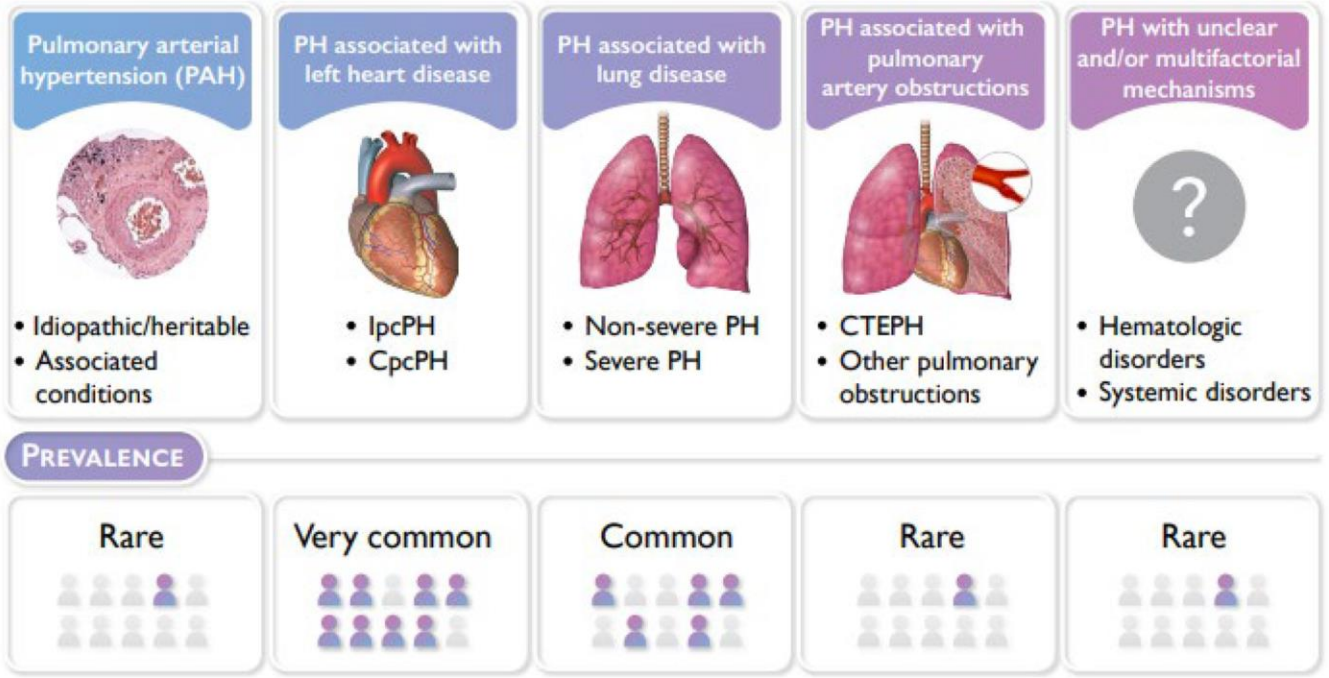
Topics

- Classification updates
- Methamphetamine induced PAH

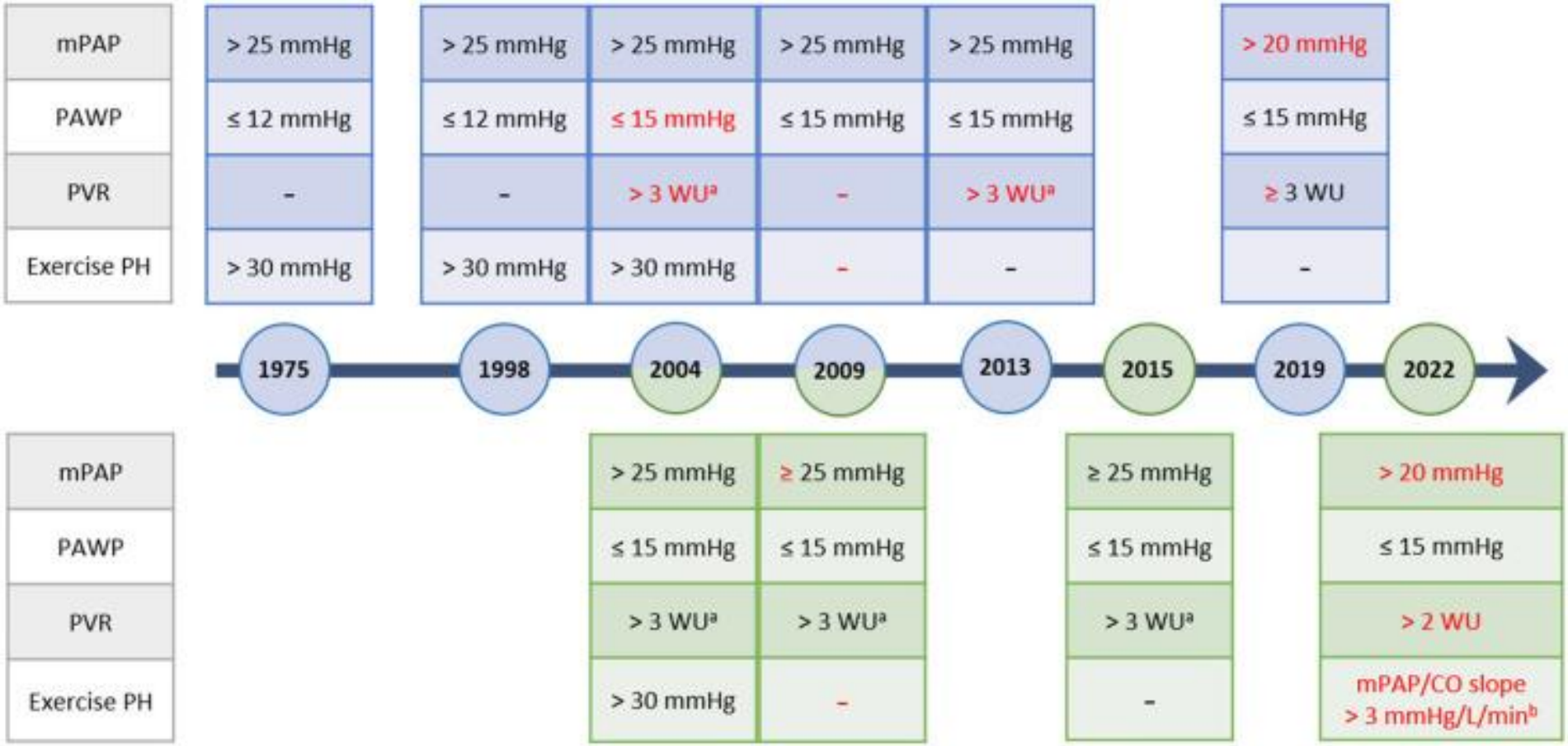


Bradley A. Maron. Journal of the American Heart Association. Revised Definition of Pulmonary Hypertension and Approach to Management: A Clinical Primer, Volume: 12, Issue: 8, DOI: (10.1161/JAHA.122.029024)

Reveal 2.0 Risk Calculator

WHO group I subgroup	PAH-CTD +1	FPAH +2	PAH-PoPH +3
Demographics and comorbidities	eGFR<60 ml/min +1	Male>60 years +2	
NYHA/WHO functional class	I -1	III +1	IV +2
Vital signs	SBP<110 mmHg +1	HR>96 bpm +1	
Hospitalization for any cause within 6 months	YES +1		
6MWT	≥440 m -2	440-320 m -1	<165 m +1
BNP	<50 pg/mL -2	200-800 pg/mL +1	>800 pg/mL +2
Pericardial effusion on Echocardiogram	YES +1		
DLCO on Pulmonary function test	<40% +1		
mRAP within 1 year on RHC	>20 mmHg +1		
PVR on RHC	<5 WU -1		

Diagnostic Threshold Timeline



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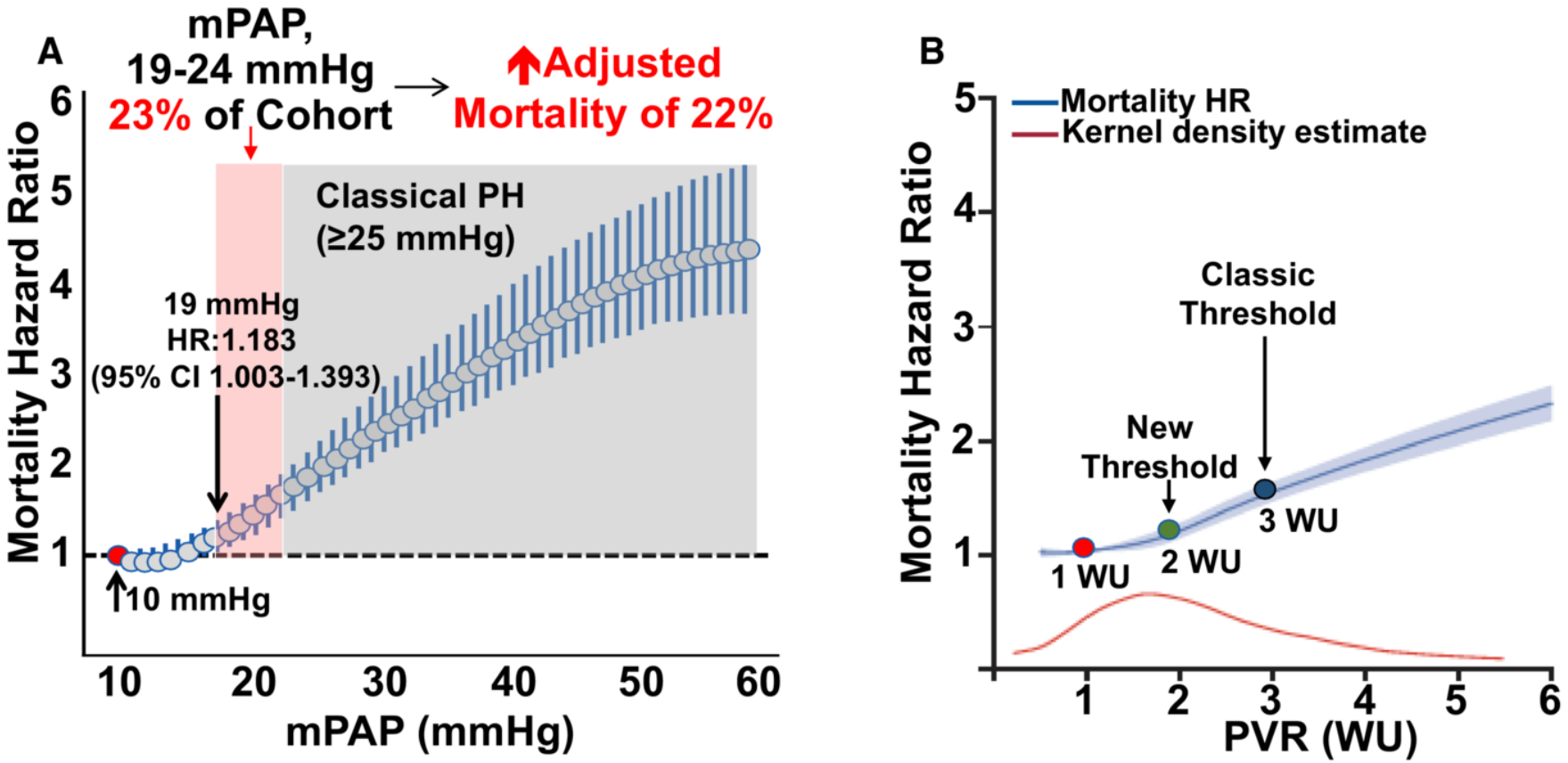

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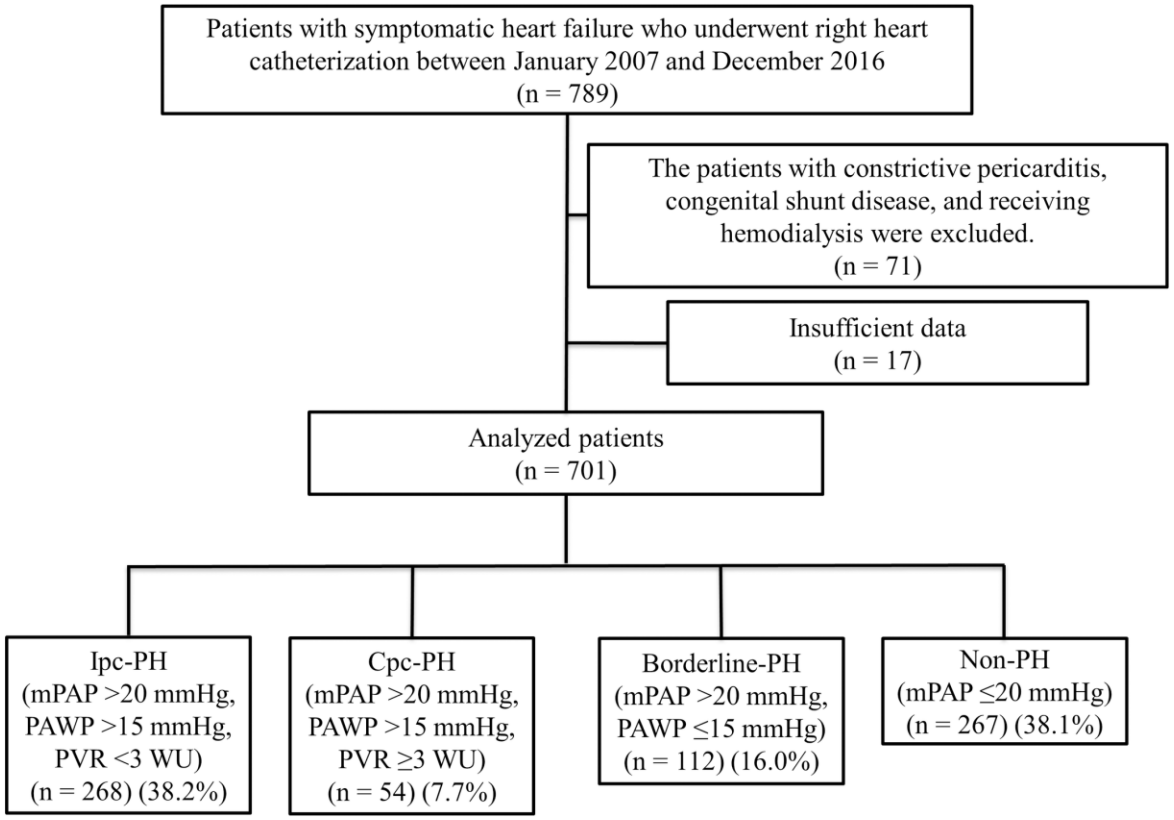
Hemodynamic definitions of pre- and post-capillary pulmonary hypertension

Definition	Haemodynamic characteristics
PH	▪ mPAP >20 mmHg
Pre-capillary PH	▪ mPAP >20 mmHg ▪ PAWP ≤15 mmHg ▪ PVR >2 WU
IpcPH	▪ mPAP >20 mmHg ▪ PAWP >15 mmHg ▪ PVR ≤2 WU
CpcPH	▪ mPAP >20 mmHg ▪ PAWP >15 mmHg ▪ PVR >2 WU
Exercise PH	▪ mPAP/CO slope between rest and exercise ▪ >3 mmHg/L/min

Some patients present with elevated mPAP (>20 mmHg) but low PVR (≤2 WU) and low PAWP (≤15 mmHg); this haemodynamic condition may be described by the term 'unclassified PH'.

PH: pulmonary hypertension; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; IpcPH: isolated post-capillary pulmonary hypertension; CpcPH: combined post- and pre-capillary pulmonary hypertension; WU: Wood units; CO: cardiac output.

A pulmonary capillary wedge pressure (PCWP) ≥15 mmHg at rest or >18 mmHg immediately after fluid challenge is considered diagnostic of LHD



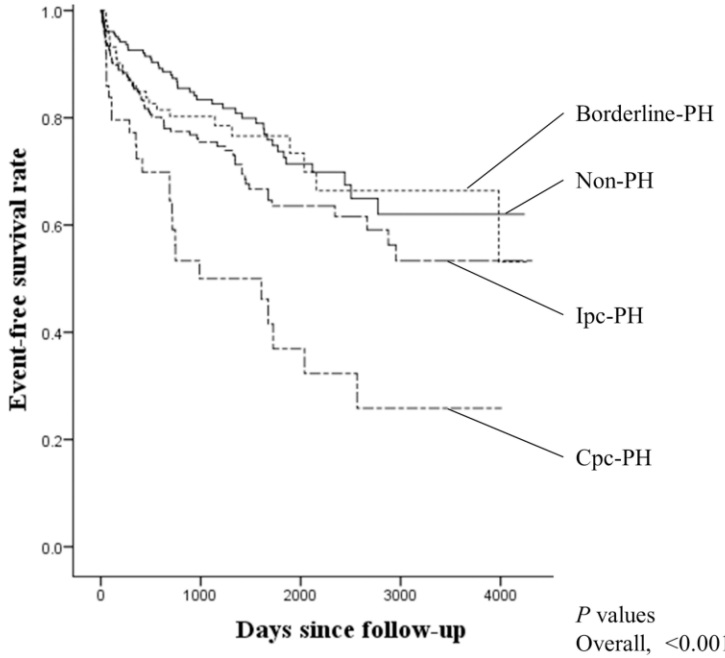
https://doi.org/10.1371/journal.pone.0247987

	Ipc-PH (n = 268)	Cpc-PH(n = 54)	Borderline-PH (n = 112)	Non-PH (n = 267)	*P* value
RAP (mmHg)	10.5 ± 4.8	12.5 ± 5.4	7.2 ± 2.8 (n = 111)	5.2 ± 2.6 (n = 266)	<0.001
sPAP (mmHg)	43.2 ± 9.8	58.0 ± 14.5	35.0 ± 5.5	26.2 ± 4.7	<0.001
mPAP (mmHg)	30.3 ± 6.6	40.3 ± 8.9	23.4 ± 2.6	16.4 ± 2.8	<0.001
dPAP (mmHg)	21.8 ± 5.9	28.2 ± 7.1	15.8 ± 2.7	10.8 ± 2.6	<0.001
PAWP (mmHg)	22.6 ± 5.6	24.0 ± 5.9	12.8 ± 2.2	9.7 ± 3.0 (n = 266)	<0.001
CO (L/min)	4.9 ± 1.4	3.9 ± 1.0	5.0 ± 1.4 (n = 108)	4.8 ± 1.2 (n = 262)	<0.001
CI (L/min/m2)	2.9 ± 0.8	2.4 ± 0.7	3.1 ± 0.8 (n = 108)	2.9 ± 0.7 (n = 262)	<0.001
Heart rate (beats/min)	77.9 ± 17.5 (n = 266)	80.3 ± 13.8 (n = 53)	71.2 ± 14.2 (n = 109)	70.4 ± 14.3 (n = 256)	<0.001
PVR (Wood units)	1.6 ± 0.6	4.2 ± 1.4	2.3 ± 0.9 (n = 108)	1.5 ± 0.7 (n = 262)	<0.001
DPG (mmHg)	-0.8 ± 3.7	4.2 ± 4.7	3.0 ± 3.2	1.0 ± 2.5 (n = 266)	<0.001
TPG (mmHg	7.8 ± 3.3	16.3 ± 5.4	10.6 ± 3.2	6.7 ± 2.4 (n = 266)	<0.001

Ipc-PH, isolated post-capillary pulmonary hypertension; Cpc-PH, combined pre- and post-capillary pulmonary hypertension; PH, pulmonary hypertension; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; DPG, diastolic pressure gradient; TPG, transpulmonary pressure gradient.

https://doi.org/10.1371/journal.pone.0247987.t002

Combined Pre and Post Pulmonary Hypertension



No. at risk					
Non-PH	267	113	53	18	3
Borderline-PH	112	51	22	9	4
Ipc-PH	268	108	44	17	1
Cpc-PH	54	15	8	2	1

P values
Overall, <0.001
Non-PH vs. Borderline-PH, 0.52
Non-PH vs. Ipc-PH, 0.03
Non-PH vs. Cpc-PH, <0.001
Borderline-PH vs. Ipc-PH, 0.27
Borderline-PH vs. Cpc-PH, <0.001
Ipc-PH vs. Cpc-PH, 0.001

- Universally worse outcomes for combined pre and post capillary PH

https://doi.org/10.1371/journal.pone.0247987

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Therapeutics for Combined Pre and Post

- MELODY-1 (ERA)
- HEART (ERA)
- EARTH (ERA)
- RELAX
- SOVIAC
- FREEDOM
- TRIMUMPH1
- FIRST
- STEP
- GRIPHON
- PATENT-1
- PATENT -2
- CHEST-1
- CHEST-2
- SOCRATES-REDUCED
- SOCRATES-PRESERVED
- LEPHT
- VICTORIA
- VITALITY
- DILATE

Key Takeaways for WHO Group 2 Pre and Post Capillary Pulm htn…..

- New subset of WHO 2 patients representing 7-15% of WHO 2 patients
- DPG replaced by PVR in diagnosis
- Worse clinical outcomes including mortality and variety of usual CHF endpoints
- No clear therapeutic benefit of directed PAH medications
- Future considerations for Sotatercept (Activin signal pathway (SOTERIA, HYPERION, ZENITH, CADENCE, MK - 7962-020, and MOONBEAM, PULSAR)

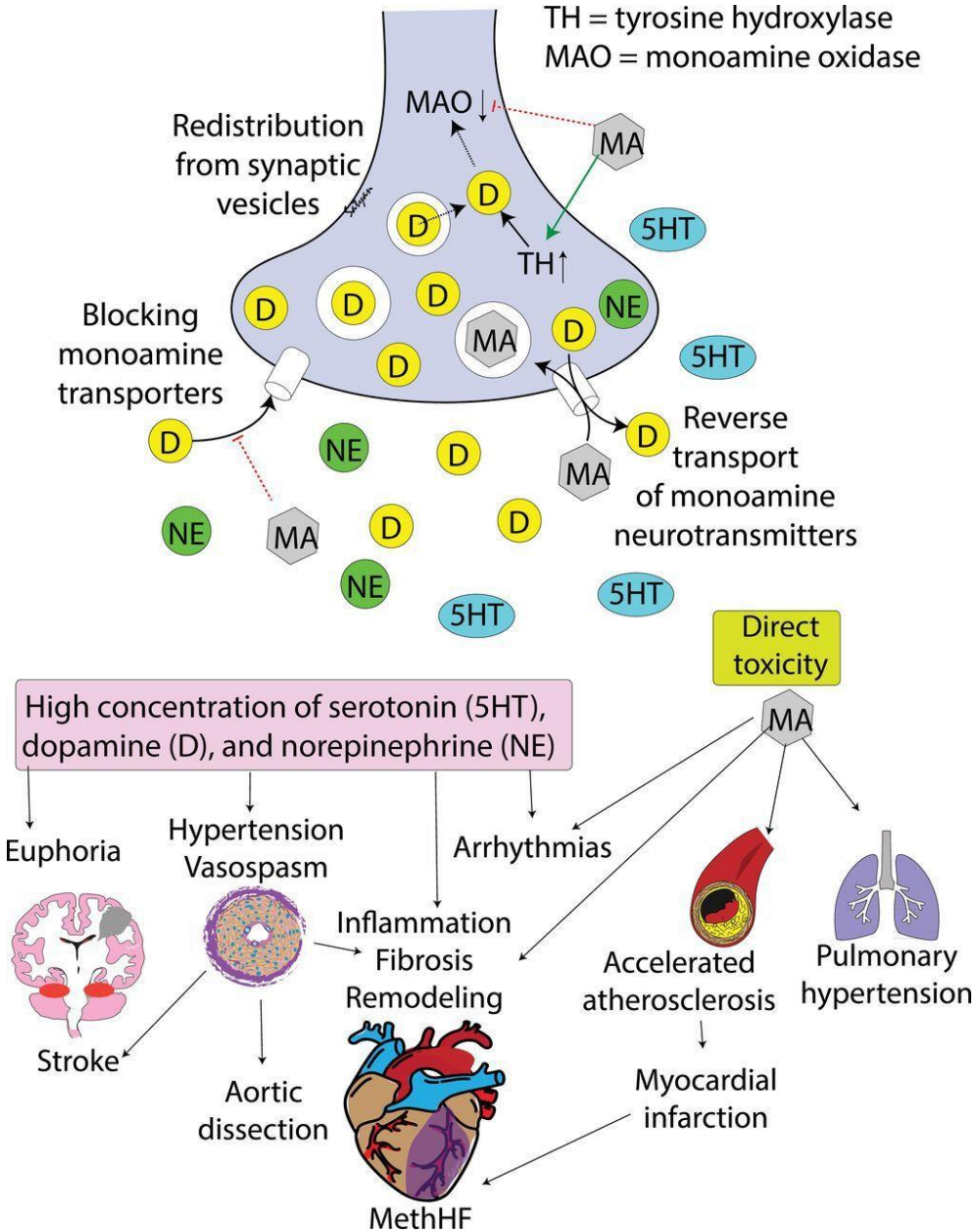
Methamphetamine

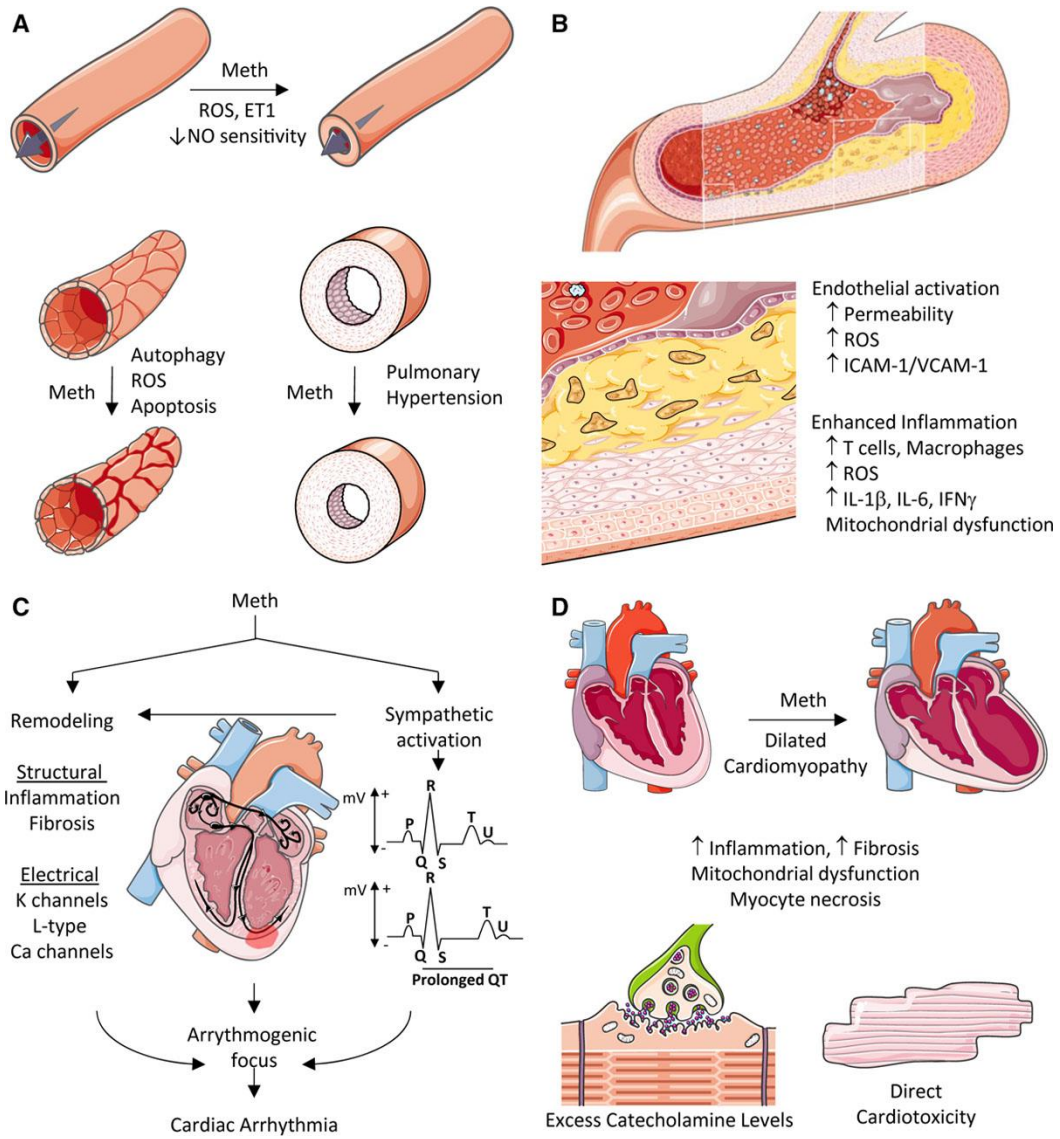
- 1972 Aminorex removed from market in Europe (WHO)
- 10-year follow up studies showed half of patients died of RHF

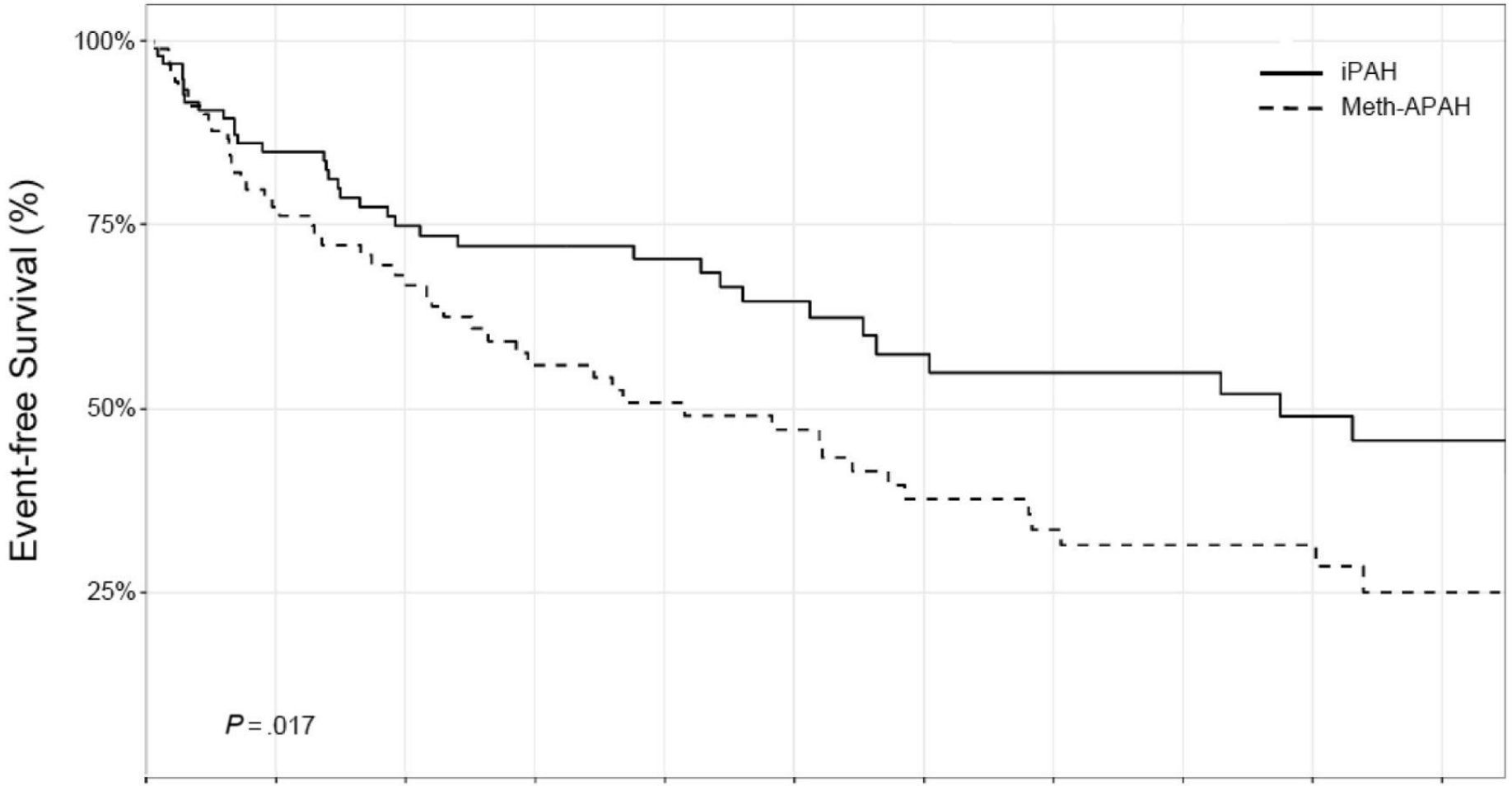
- Fen-Phen 1996, removed 1997
- 20% of 73 pt in 1993 review suggested Fen use

HP Gurtner Core Vasa 1985;27(2-3):160-71
Brenot et al Br Heart Journal 1993 Dec;70 (6);537-41

Physiology


TH = tyrosine hydroxylase
MAO = monoamine oxidase
Redistribution from synaptic vesicles
MAO
MA
D
5HT
TH
NE
Blocking monoamine transporters
Reverse transport of monoamine neurotransmitters
High concentration of serotonin (5HT), dopamine (D), and norepinephrine (NE)
Direct toxicity
Euphoria
Hypertension
Vasospasm
Arrhythmias
Inflammation
Fibrosis
Remodeling
Accelerated atherosclerosis
Pulmonary hypertension
Stroke
Aortic dissection
Myocardial infarction
MethHF


A
Meth
ROS, ET1
↓NO sensitivity
Meth
Autophagy
ROS
Apoptosis
Meth
Pulmonary Hypertension
B
Endothelial activation
↑ Permeability
↑ ROS
↑ ICAM-1/VCAM-1
Enhanced Inflammation
↑ T cells, Macrophages
↑ ROS
↑ IL-1β, IL-6, IFNγ
Mitochondrial dysfunction
C
Meth
Remodeling
Structural
Inflammation
Fibrosis
Electrical
K channels
L-type
Ca channels
Sympathetic activation
mV
R
P
T
U
Q
S
Prolonged QT
Arrythmogenic focus
Cardiac Arrhythmia
D
Meth
Dilated Cardiomyopathy
↑ Inflammation, ↑ Fibrosis
Mitochondrial dysfunction
Myocyte necrosis
Excess Catecholamine Levels
Direct Cardiotoxicity

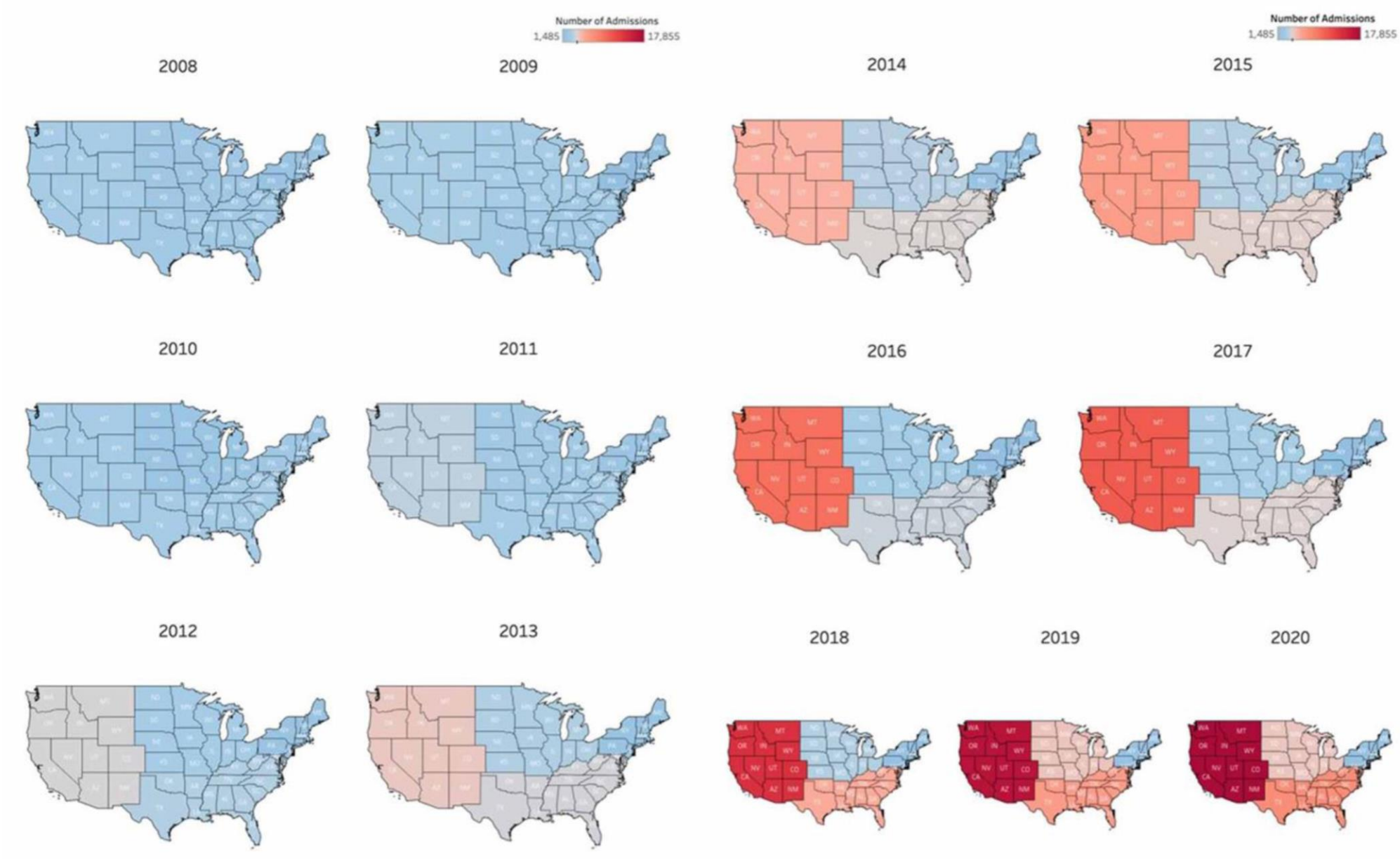


Number at Risk

iPAH	97	72	57	45	40	30	23	20	20	16	11
Meth-APAH	90	64	48	34	28	25	20	16	13	12	4

Zamanian 2018. American Journal Resp and Crit Care Medicine Vol 197 Number 6

Cardiomyopathy-Associated Hospital Admissions Among Methamphetamine Users by Region from 2008-2020



Case Presentation

- 38 yo female presents to ED with sob and abd distension.
- Smoker, Asthma
- Notes 20lbs weight gain over last 2m
- RV markedly increased, systolic function markedly reduced, RVSP 99 mmHg, TAPSE 1.1, EF 65%, LA normal size.

- mPAP 54mmHg
- Wedge 4 mm Hg
- PA sat 59%
- RA 10 mmHg
- CI 1.66 (Fick)

Case Presentation

- 3 separate admissions at local facilities
- Liver eval suggested cirrhosis
- Saw PCP 4x in last two years with inhalers changes, smoking discussion
- Cholecystectomy

- Currently on triple therapy
- Dry weight
- Zero admissions
- Still struggling with meth use and missed appointments

Methamphetamine-PAH Takeaways

- Use on the rise
- Worse outcomes vs IPAH
- Can persist even with cessation of drug
- Similar physiology to PAH

- Unique care perspectives from PH clinic (i.e. give a little grace)

"In my younger years and more vulnerable years, my father gave me some advice that I've been turning over in my mind ever since. 'Whenever you feel like criticizing anyone, just remember that all the people in this world haven't had the same advantages that you've had.'"

Thank You