Have we found the pulmonary circulation's ramipril?

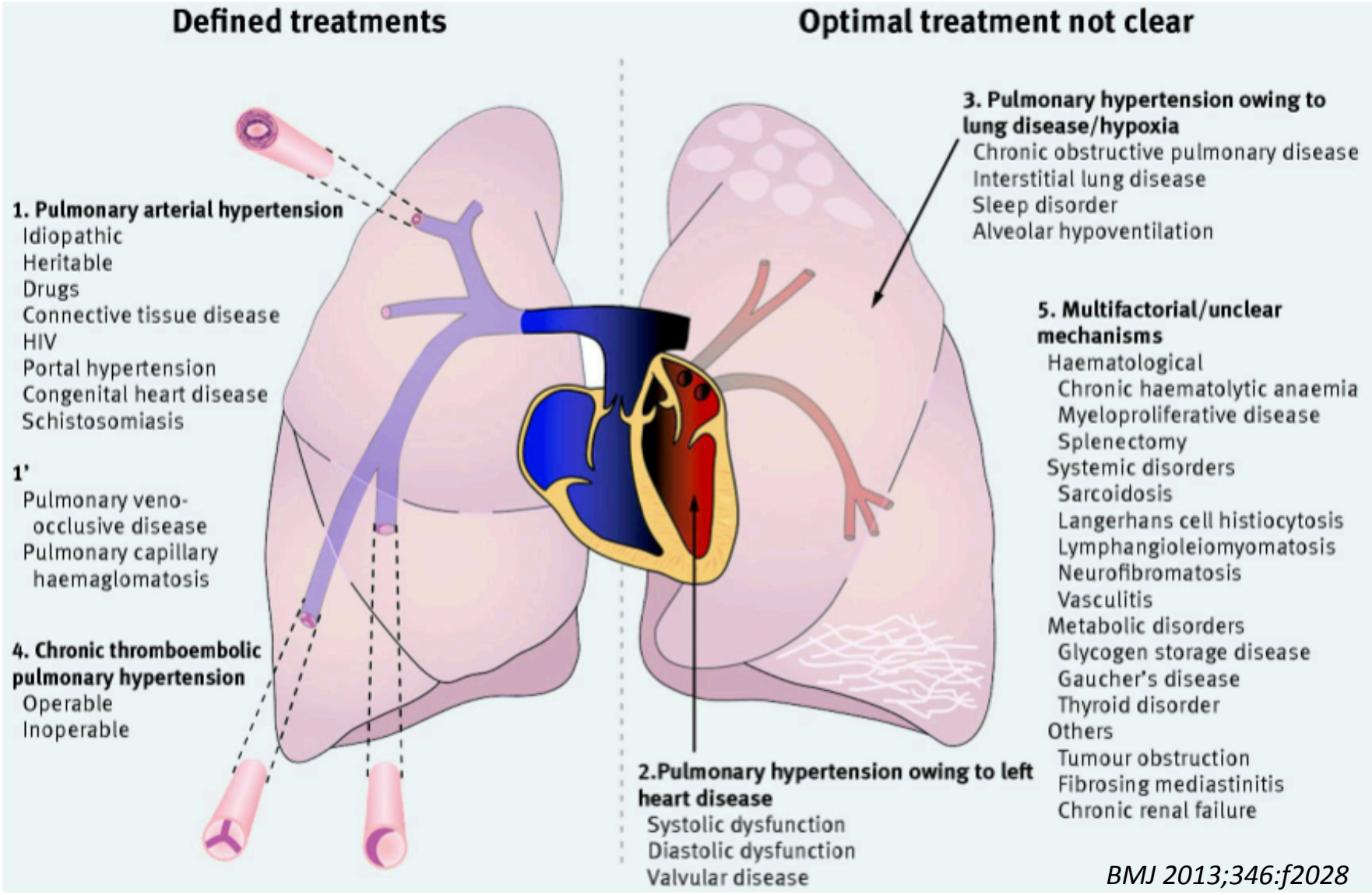
Macitentan for Pulmonary Arterial Hypertension

by Ricky Turgeon

Pulmonary Hypertension

- Increased resistance within the pulmonary vasculature
  - Defined as mean pulmonary artery pressure (PAM) ≥25 mmHg at rest or ≥30 mmHg with exercise

Etiologies of PH
(2003 WHO Classification)



BMJ 2013;346:f2028

Pulmonary Arterial Hypertension (PAH)

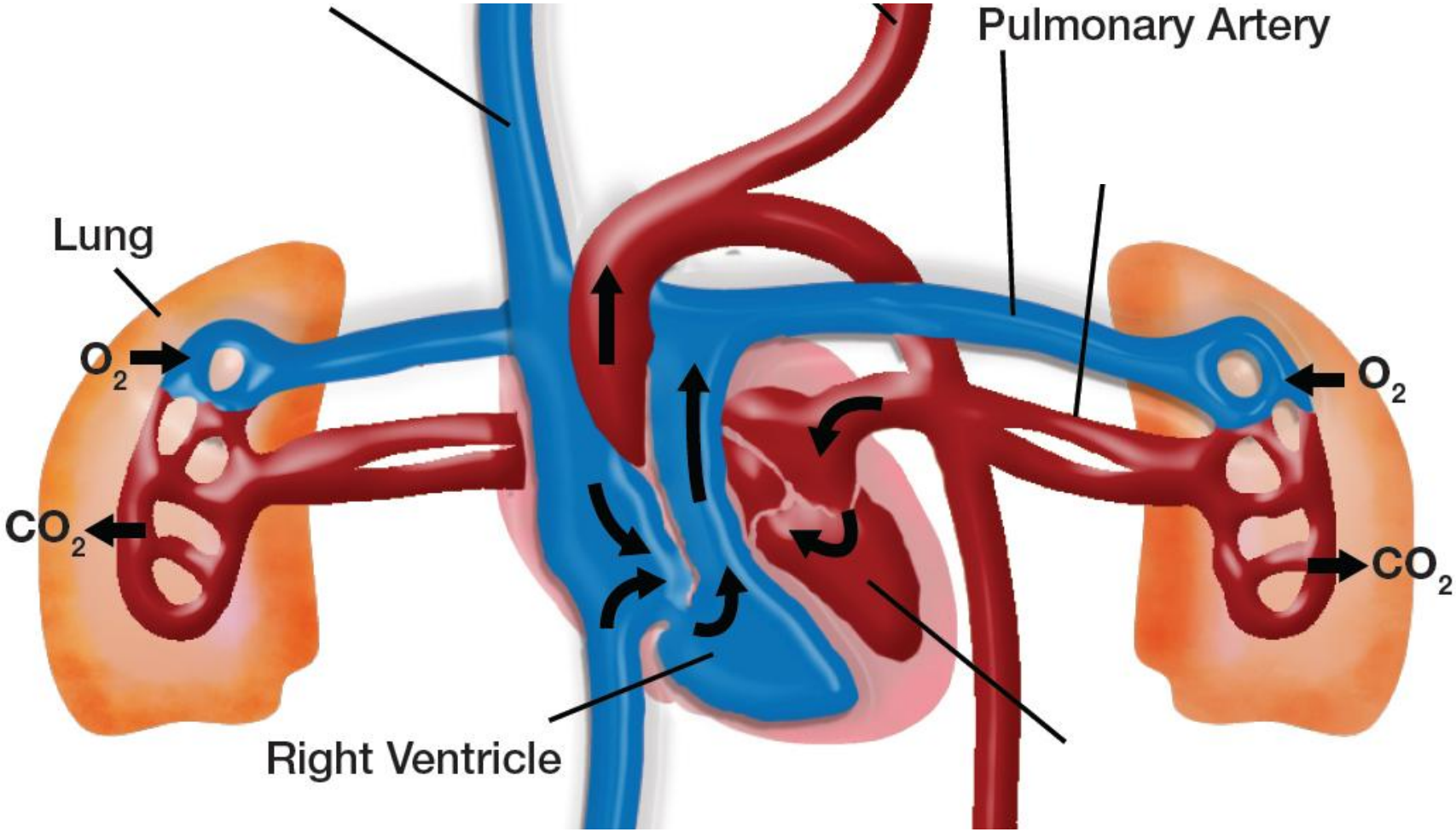


Image from www.caymanchem.com/images/articles/page/2210-1.jpg

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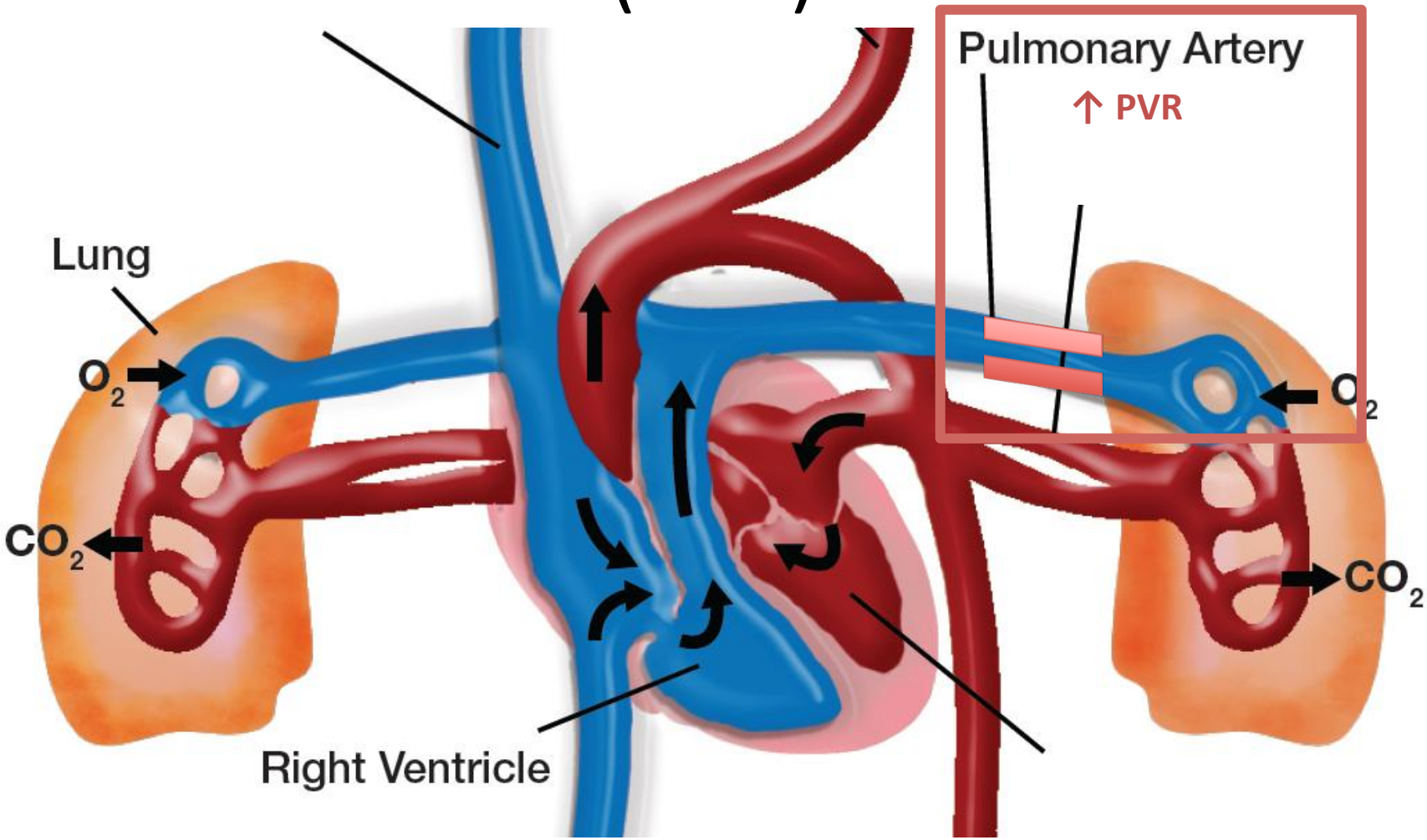

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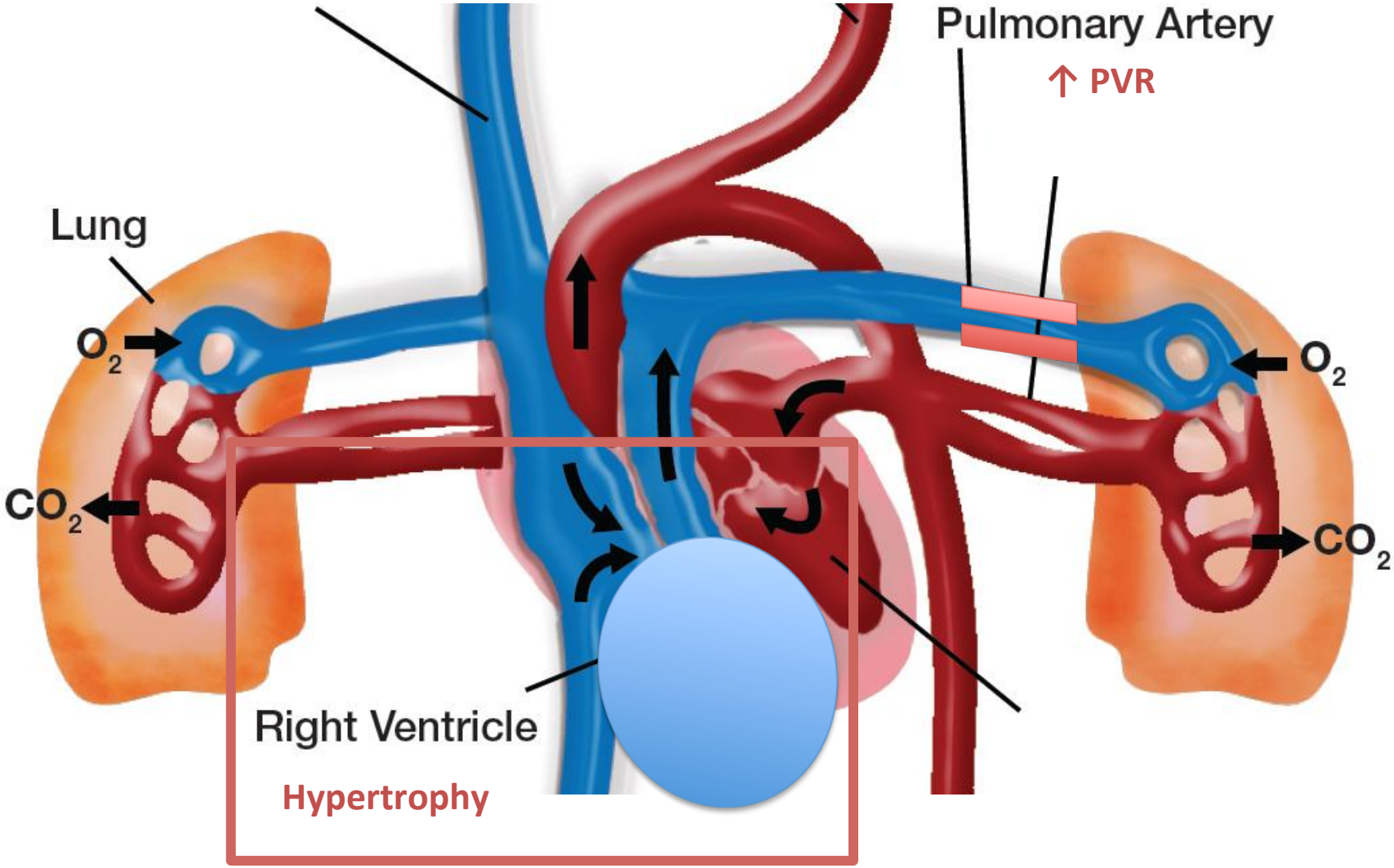

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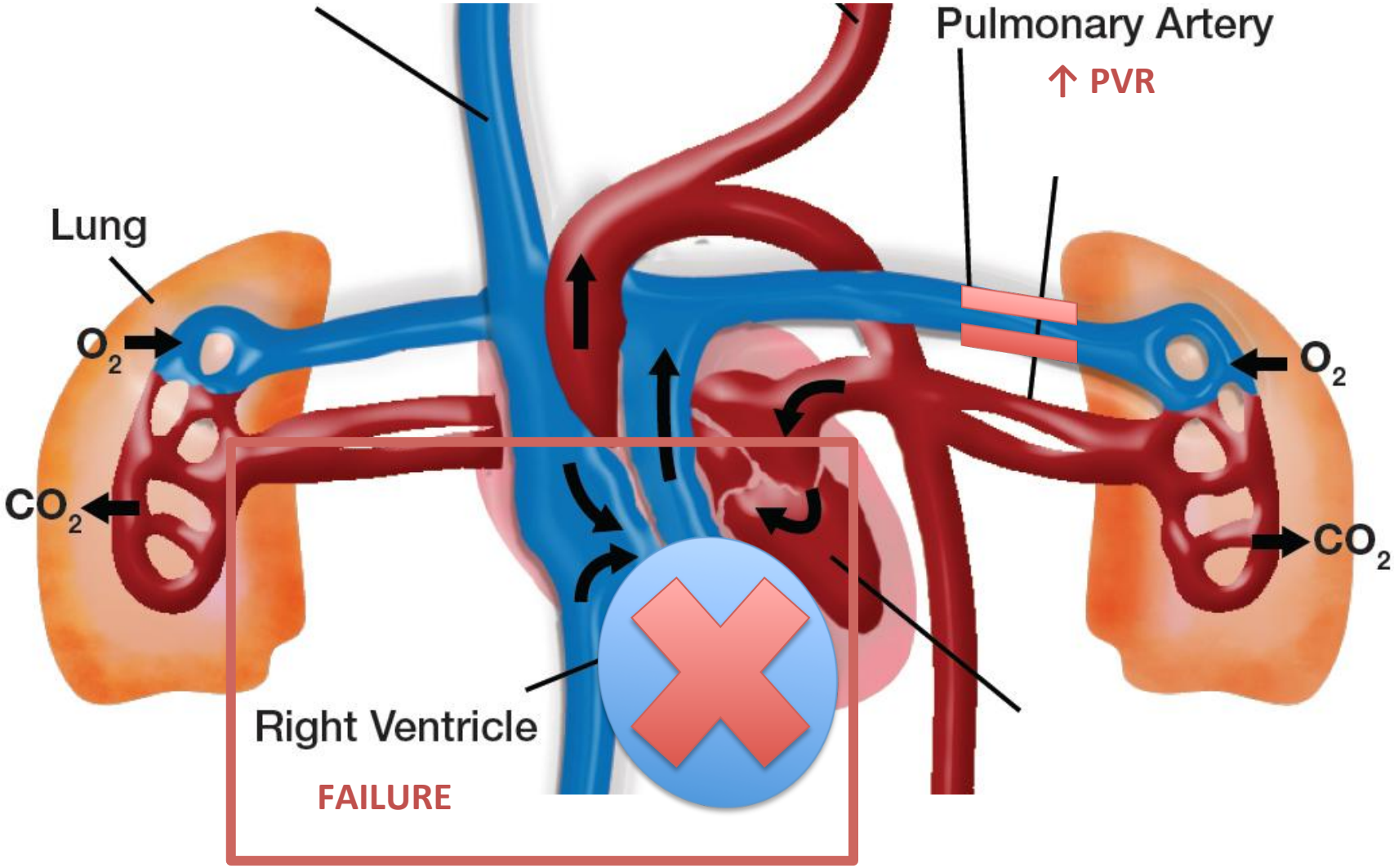

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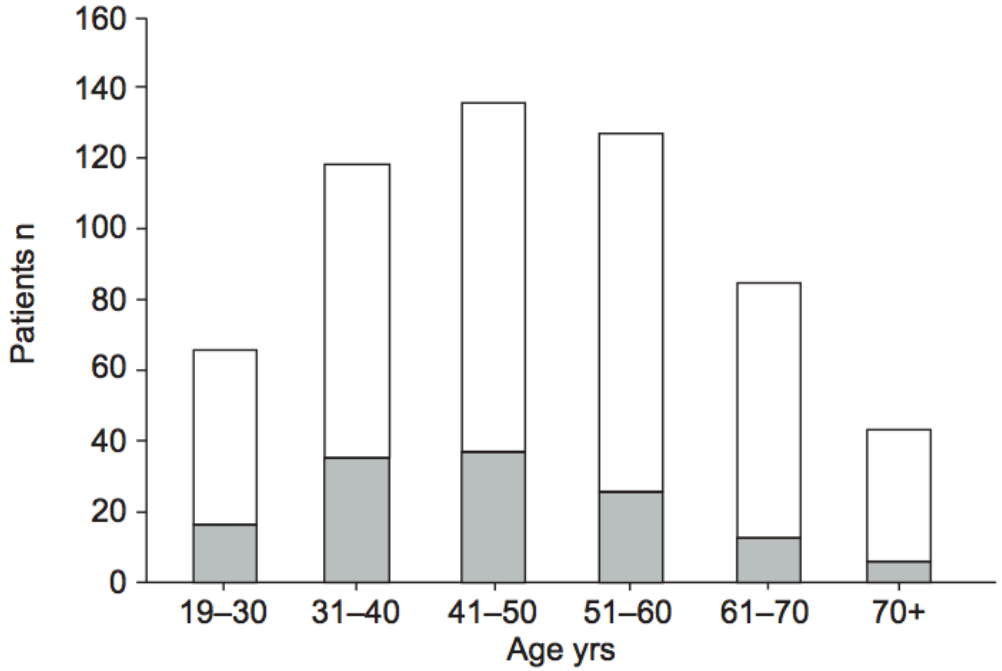
PAH: Epidemiology

Prevalence: 15 cases per million

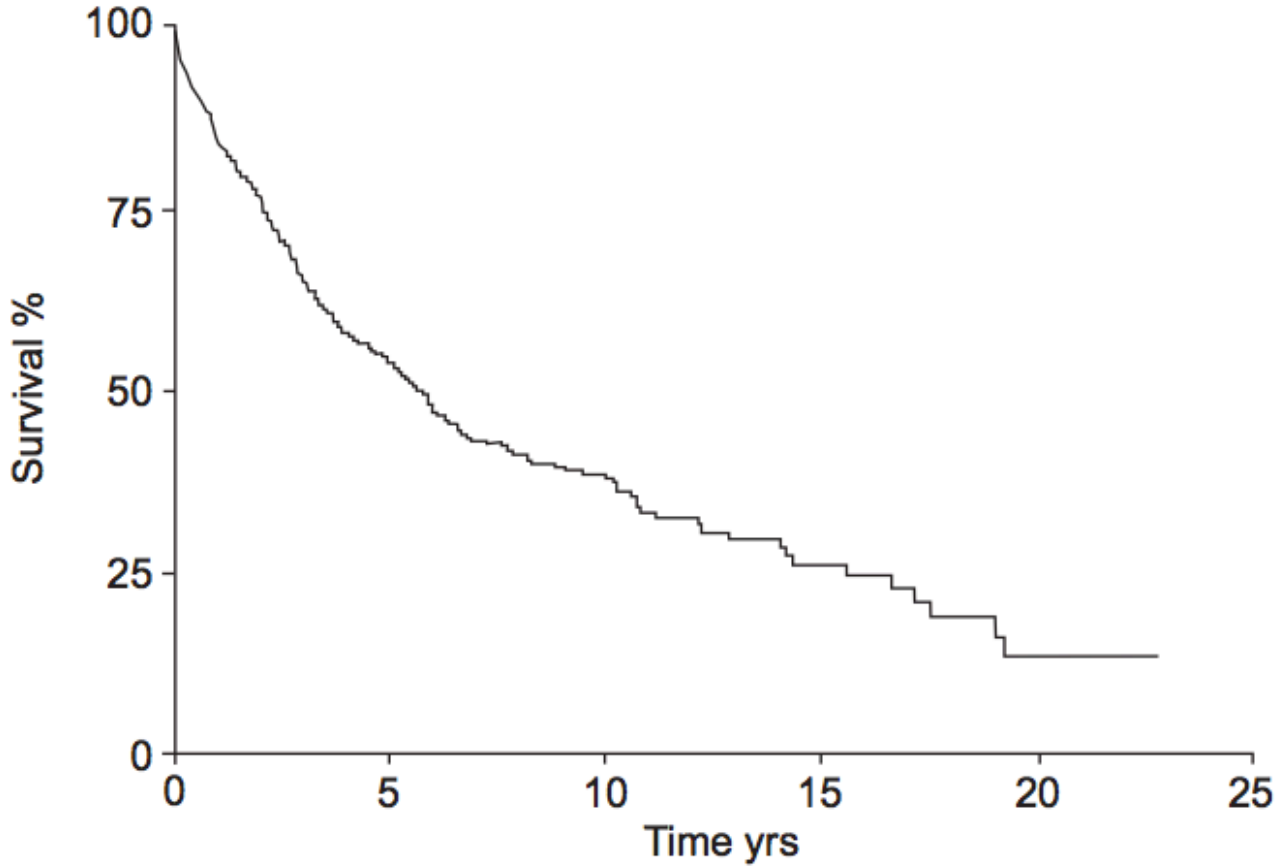
Mean age at diagnosis: 50 years



Eur Respir J 2007;30:1103-10
JACC 2009;53:1573-619

PAH: Epidemiology

Prognosis *with treatment*:



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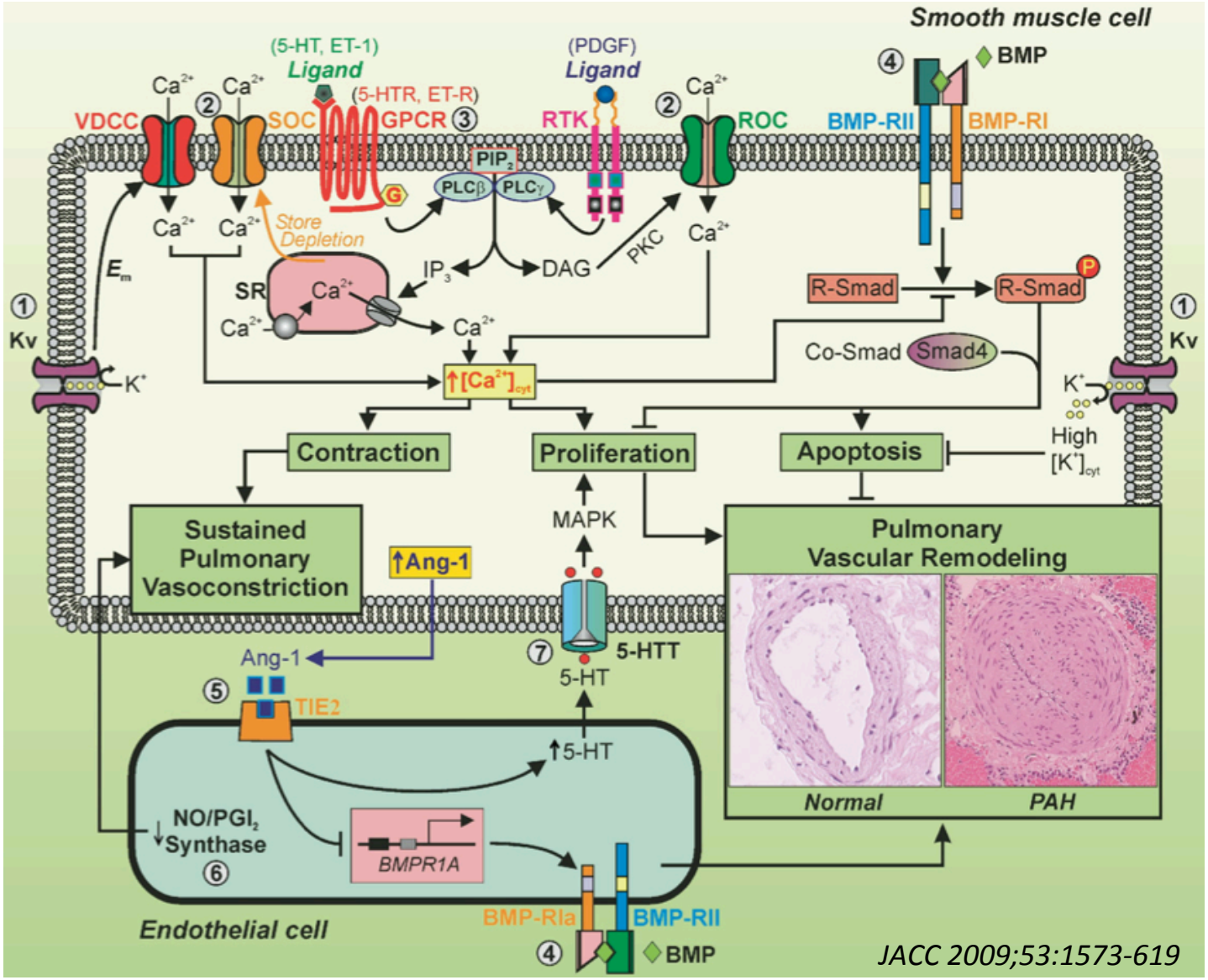
Mechanisms & Potential Targets



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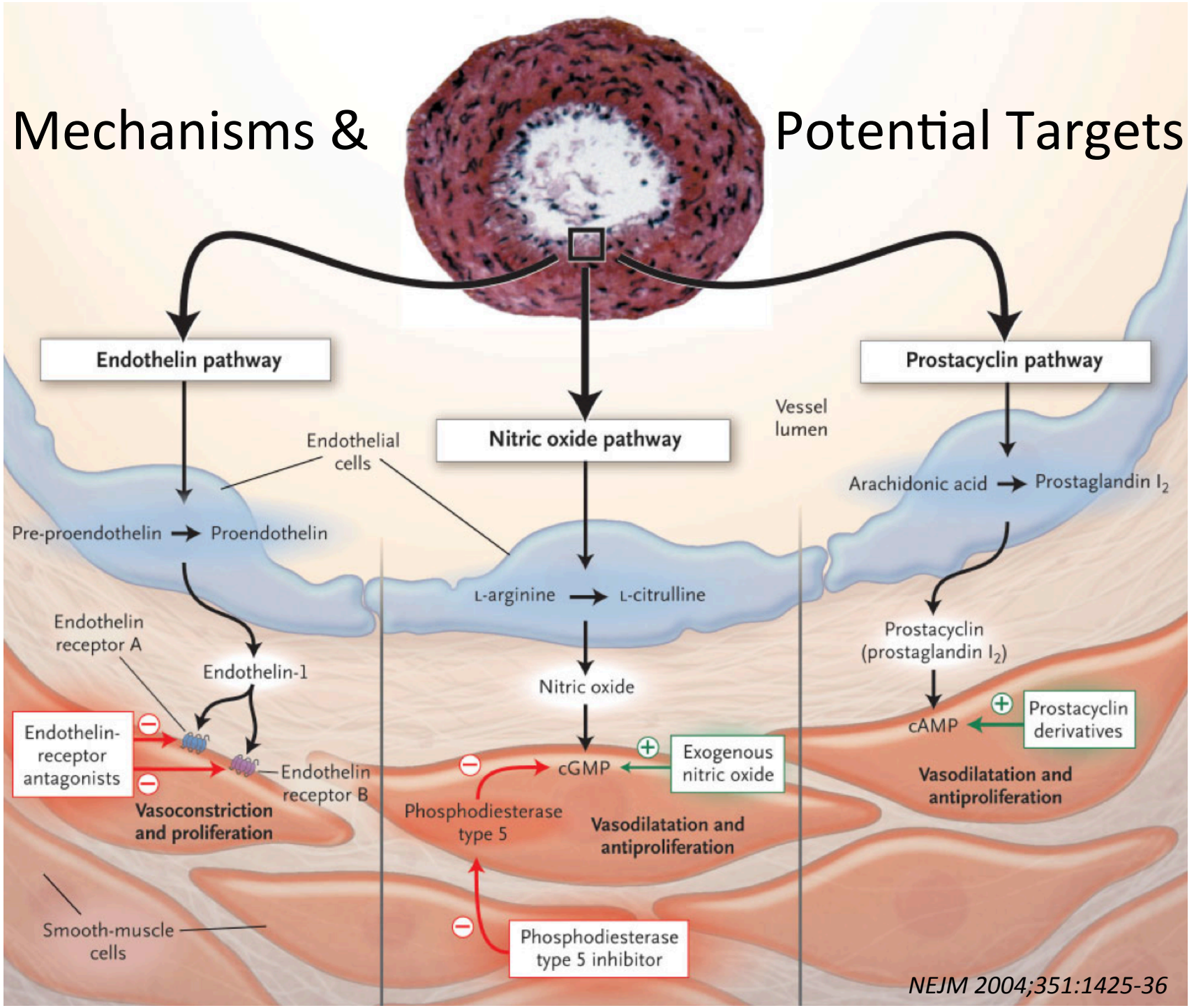
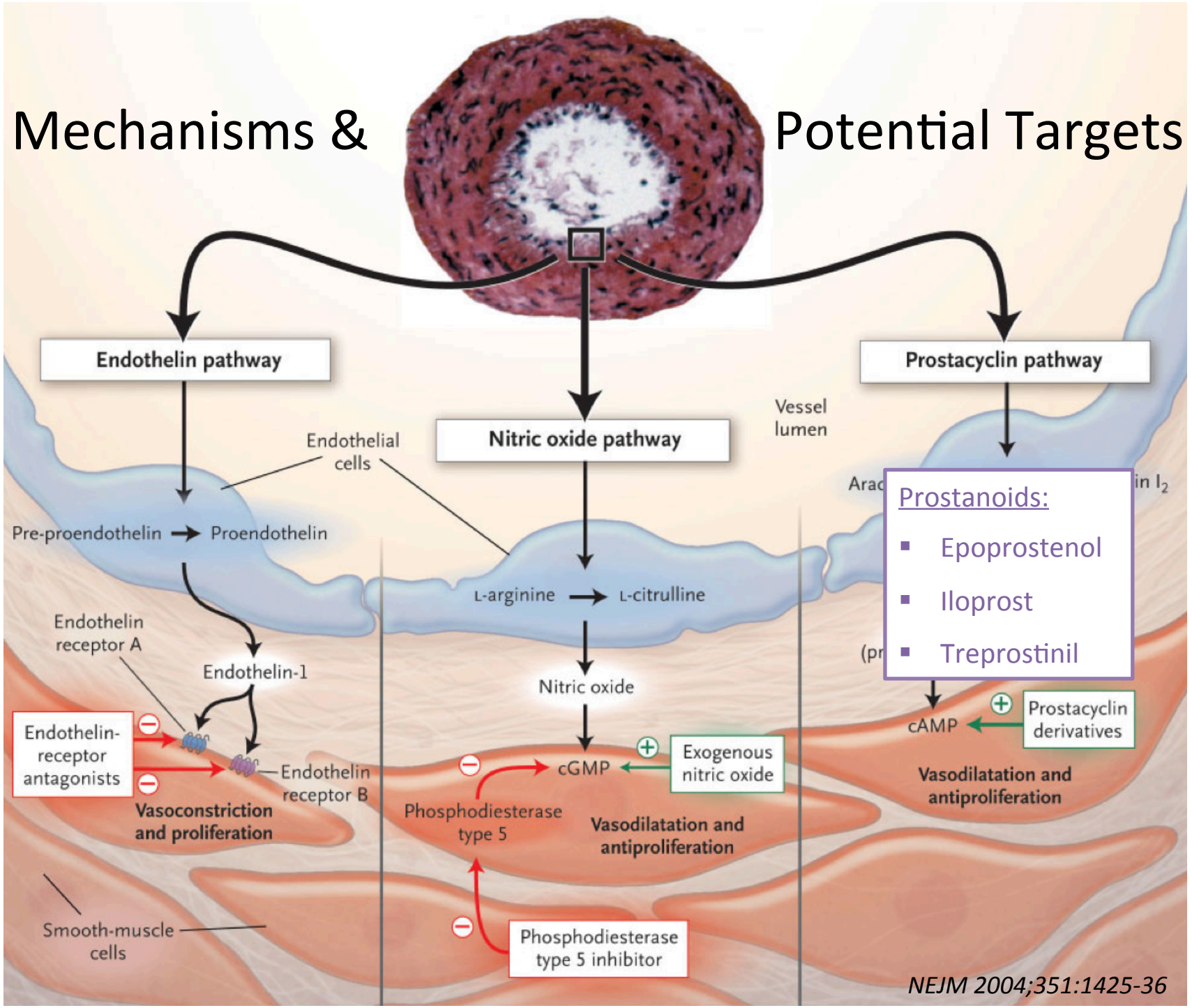
Mechanisms & Potential Targets



NEJM 2004;351:1425-36

Mechanisms & Potential Targets



NEJM 2004;351:1425-36

Prostanoids

Efficacy (vs placebo/control)

- Mortality 51% RRR
  - *Mainly due to single epoprostenol RCT*
- Functional class improvement
  - RR 3.39, 95% CI 1.56-7.36

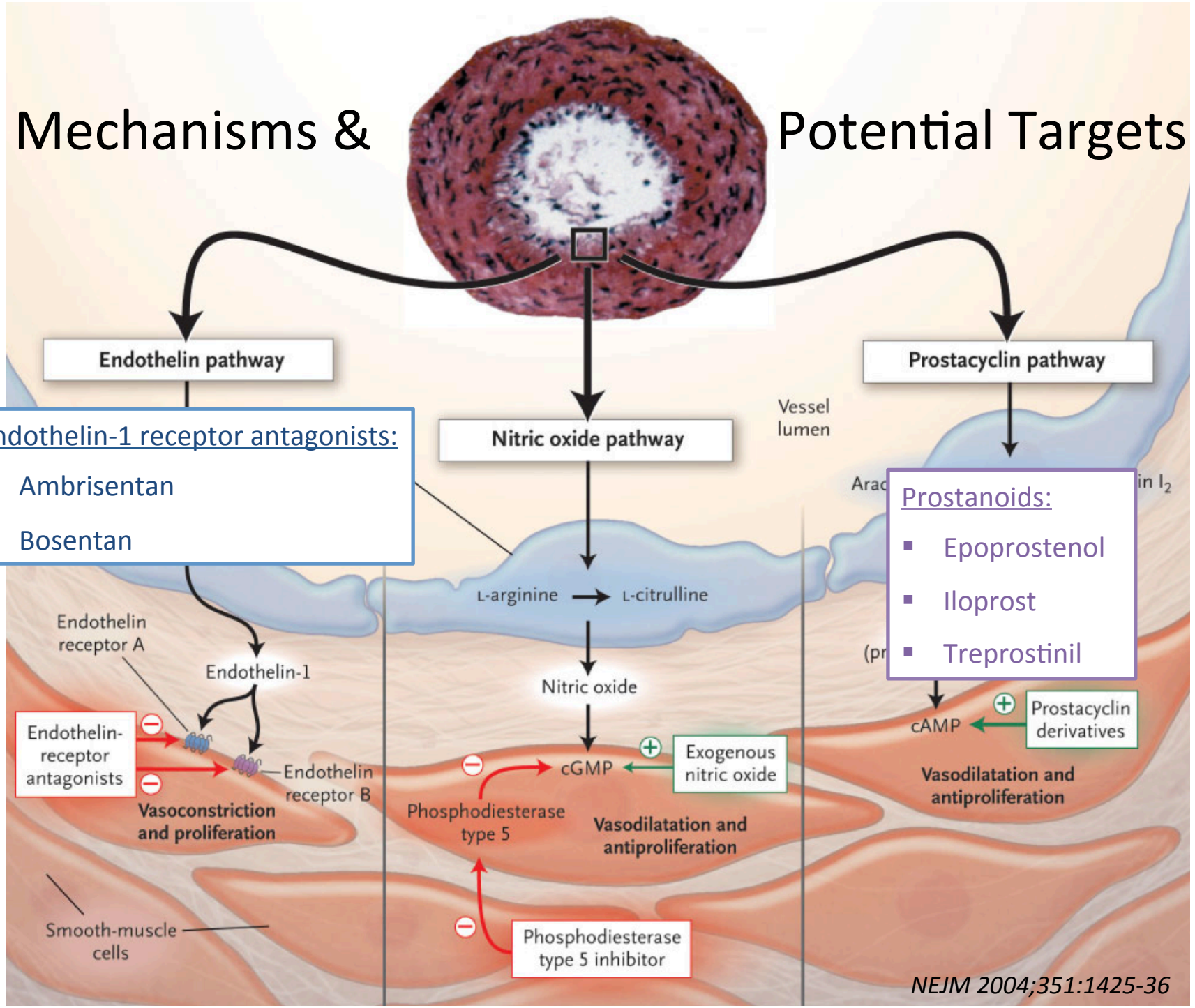
Respir Res 2010;11:12

Prostanoids

	Administration	Cost/year
Epoprostenol	Continuous IV infusion	~$33k (70kg, low dose)
Iloprost	Inhalation 6-9x/day	~$57k
Treprostinil	Inhaled QID or Continuous subcut/IV infusion	~$98k (70kg, low dose)

JACC 2009;53:1573-619
Respir Res 2010;11:12

Mechanisms & Potential Targets



Endothelin-1 receptor antagonists:

- Ambrisentan
- Bosentan

Prostanoids:

- Epoprostenol
- Iloprost
- Treprostinil

NEJM 2004;351:1425-36

Endothelin-1 Receptor Antagonists

Efficacy (vs placebo/control)

- No significant effect on mortality
  - RR 0.58, 95% CI 0.21-1.60
- Functional class improvement
  - RR 1.67, 95% CI 1.23-2.29

Respir Res 2010;11:12

Endothelin-1 Receptor Antagonists

Safety

- HEME:
  - Anemia
- LIVER:
  - LFT elevations (rare hepatotoxicity)

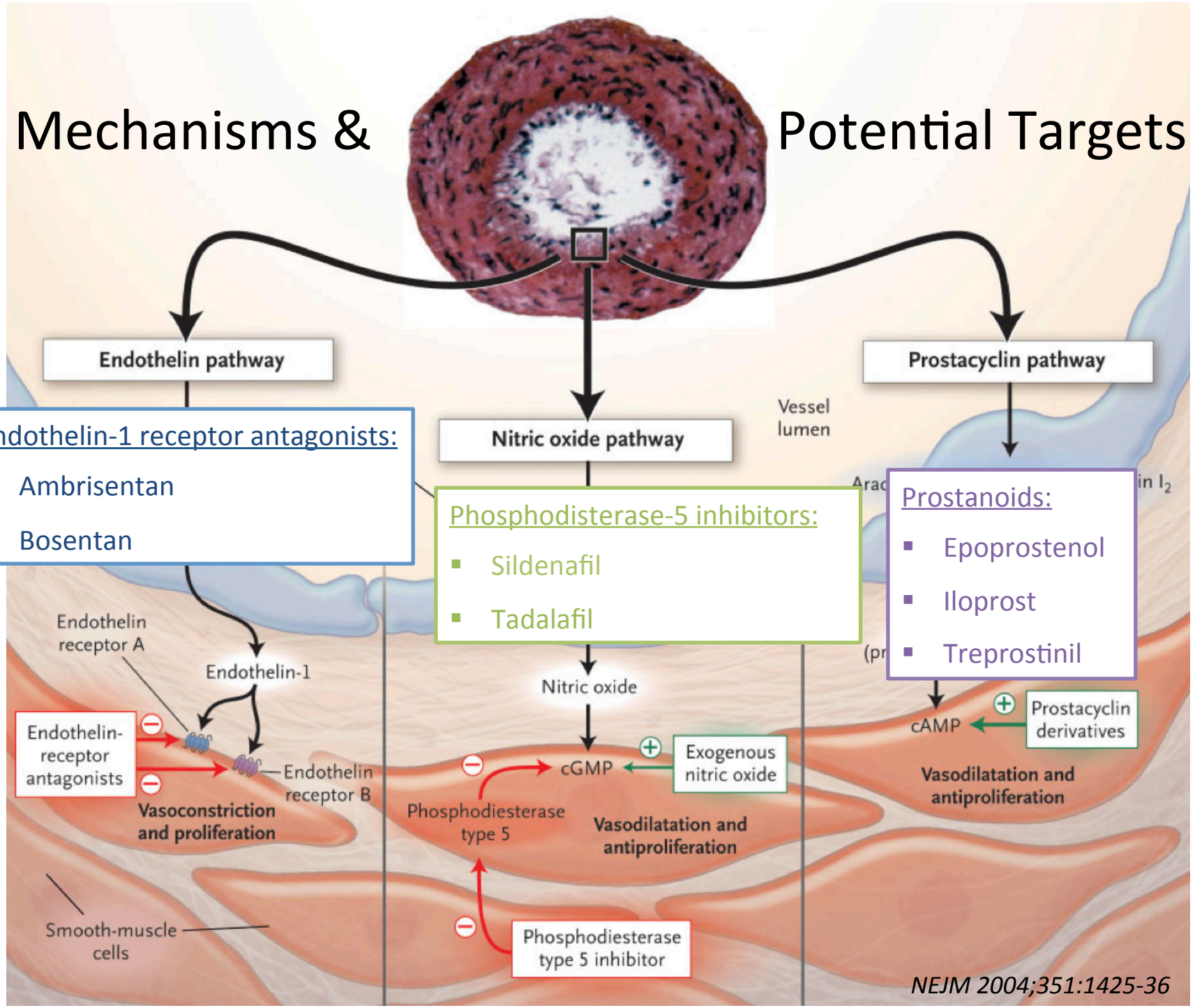
Respir Res 2010;11:12

Endothelin-1 Receptor Antagonists

	Administration	Cost/year
Ambrisentan	PO once daily	~$57k
Bosentan	PO BID	~$55k

JACC 2009;53:1573-619
Respir Res 2010;11:12

Mechanisms & Potential Targets



Endothelin-1 receptor antagonists:

- Ambrisentan
- Bosentan

Phosphodisterase-5 inhibitors:

- Sildenafil
- Tadalafil

Prostanoids:

- Epoprostenol
- Iloprost
- Treprostinil

NEJM 2004;351:1425-36

Phosphodiesterase-5 Inhibitors

Efficacy (vs placebo/control)

- No significant effect on mortality
  - RR 0.30, 95% CI 0.08-1.08
- Functional class improvement: ~40% absolute risk increase

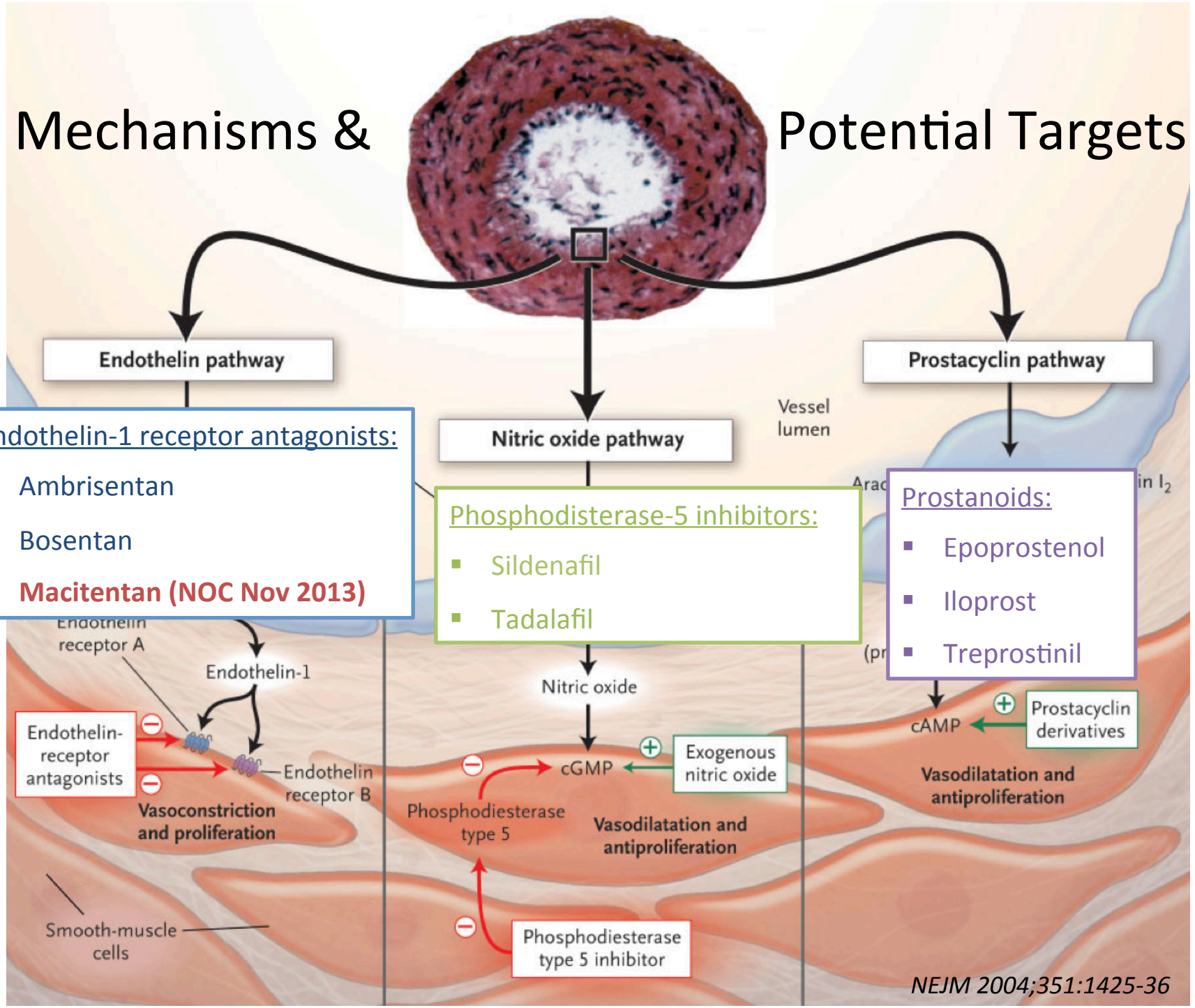
NEJM 2005;353:2148-57
Respir Res 2010;11:12

Phosphodiesterase-5 Inhibitors

	Administration	Cost/year
Sildenafil	PO TID	~$13k
Tadalafil	PO once daily	-

JACC 2009;53:1573-619
Respir Res 2010;11:12

Mechanisms & Potential Targets



Endothelin-1 receptor antagonists:

- Ambrisentan
- Bosentan
- **Macitentan (NOC Nov 2013)**

Phosphodisterase-5 inhibitors:

- Sildenafil
- Tadalafil

Prostanoids:

- Epoprostenol
- Iloprost
- Treprostinil

NEJM 2004;351:1425-36

Our Clinical Question

P	In patients with pulmonary arterial hypertension
I	does macitentan
C	vs • Existing therapies • Placebo/no therapy
O	Increase/decrease: • Mortality & morbidity related to PAH • Surrogates (functional or hemodynamic) • ADRs

Search Strategy

Databases	PubMed (N = 38) EMBASE (N = 140) CENTRAL (N = 9) Cochrane Database of Systematic Reviews (N = 1) International Pharmaceutical Abstracts (N = 4)
Search Date	Inception-Jan 14 2014
Search Terms	“macitentan”
Results	1 RCT

SERAPHIN *NEJM. 2013;369:809-18*

D	• Multicentre (151 centers, 39 countries), double-blind RCT • Median duration: 2.2 years

P	n = 742
	
	Inclusion:
	• Age ≥12 y
	• PAH
	  ○ Etiology: idiopathic, heritable, connective-tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV, drug use or toxin exposure
	  ○ Confirmed by right heart catheterization
	• WHO class II-IV (analogous to NYHA classification)
	• 6-minute walk distance 50-475 m

SERAPHIN

P	Exclusion: • PAH of other etiologies not listed in inclusion criteria • PH group 2-5 • Body weight <40 kg • Systolic BP <100 mmHg • Moderate to severe obstructive or restrictive lung disease • Liver disease • Hemoglobin <75% lower limit of normal
I/C	• Placebo • Macitentan 3 mg PO once daily • Macitentan 10 mg PO once daily

NEJM 2013;369:809-18

SERAPHIN

O	1° outcome, time to first of the following: a) All-cause mortality b) Worsening of PAH (defined as ALL 3 of the following) i. Decrease in 6-min walk distance ≥15% performed on a different day within 2 weeks ii. Worsening of symptoms of PAH ▪ Increase in WHO functional class ▪ Appearance of worsening of signs of right HF that did not respond to PO diuretic therapy iii. Need for additional treatment for PAH c) Initiation of treatment with IV or subcut prostanoids d) Lung transplantation e) Atrial septostomy

NEJM 2013;369:809-18

SERAPHIN

O	2^{o} outcomes a) 6-min walk distance change from baseline to month 6 b) % of patients with improvement in WHO functional class at 6 months c) Death or hospitalization due to PAH Cardiac hemodynamic change from baseline to 6 months (n = 145) a) Pulmonary vascular resistance (PVR) b) Cardiac index (CI) Safety outcomes • Adverse events • Laboratory abnormalities

NEJM 2013;369:809-18

Generalizability

Average patient:

- Mean age ~45.6 y
  - Time since PAH diagnosis mean 2.7 y
- Female ~75%
- Ethnicity: White 55%, Asian ~30%, Hispanic 15%, Black or other 3%

Generalizability

Average patient:

- PAH class
  - Idiopathic 55%
  - Connective-tissue disease 30%
  - Others 15%
- WHO functional class
  - II ~52%
  - III ~46%
  - IV ~2%
- Background PAH therapy ~2/3 (mostly PDE-5 inhibitors)

SERAPHIN: Internal Validity

Selection bias	• Sequence generation	?
	• Allocation concealment	Centralized automated phone or Internet randomization
Performance bias	• Blinding of patients and personnel	Indistinguishable placebo
Detection bias	• Blinding of outcome assessors and adjudicators	Yes
Attrition bias	• Addressed incomplete outcome data	ITT analysis
Reporting bias	• Free from selective outcome reporting?	No

Results

Outcome	Placebo	Macitentan 3 mg	Macitentan 10 mg	HR (95% CI) 3 mg vs placebo	HR (95% CI) 10 mg vs placebo
1º outcome	**46.4%**	**38%**	**31.4%**	**0.70 (0.52-0.96)** **NNT 12**	**0.55 (0.32-0.76)** **NNT 7**

Consistent benefit across all subgroups (all tests for interaction >0.10), including '± concomitant PAH therapies'

Results

Outcome	Placebo	Macitentan 3 mg	Macitentan 10 mg	HR (95% CI) 3 mg vs placebo	HR (95% CI) 10 mg vs placebo
1º outcome	**46.4%**	**38%**	**31.4%**	**0.70 (0.52-0.96)** **NNT 12**	**0.55 (0.32-0.76)** **NNT 7**
All-cause mortality	7.6%	8.4%	5.8%		
Lung transplant	0	0.4%	0		
Worsening of PAH	37.2%	28.8%	24.4%		
Need for prostanoid	2.4%	0.4%	0.4%		

Results

Outcome	Placebo	Macitentan 3 mg	Macitentan 10 mg	3 mg vs placebo	10 mg vs placebo
2º outcome					
6-min walk distance	-9.4 m	+7.4 m	12.5 m	p=0.01	p=0.008
Functional class improvement	13%	20%	22%	p=0.04	p=0.006
Cardiac hemodynamics baseline to 6 months					
PVR (dyn*sec/cm^5)	+156	-209	-227		
CI (L/min/m^2)	-0.33	+0.36	+0.30		

Results

Outcome	Placebo	Macitentan 3 mg	Macitentan 10 mg
Safety			
Serious AE	**55%**	**52%**	**45%**
Headache	8.8%	13.2%	13.6%
URTI	13.3%	20%	15.3%
Nasopharyngitis	10.4%	14.8%	14%
Bronchitis	5.6%	8%	11.6%
Anemia	3.2%	8.8%	13.2%
Hemoglobin ≤80 g/L	0.4%	1.7%	4.3%
ALT/AST >3x ULN	4.5%	3.6%	3.4%
ALT/AST >3x ULN + bili >2x ULN	1.7%	2.1%	1.7%

Results

Outcome	Placebo	Macitentan 3 mg	Macitentan 10 mg
Safety			
Serious AE	**55%**	**52%**	**45%**
Headache	8.8%	13.2%	13.6%
URTI	13.3%	20%	15.3%
Nasopharyngitis	10.4%	14.8%	14%
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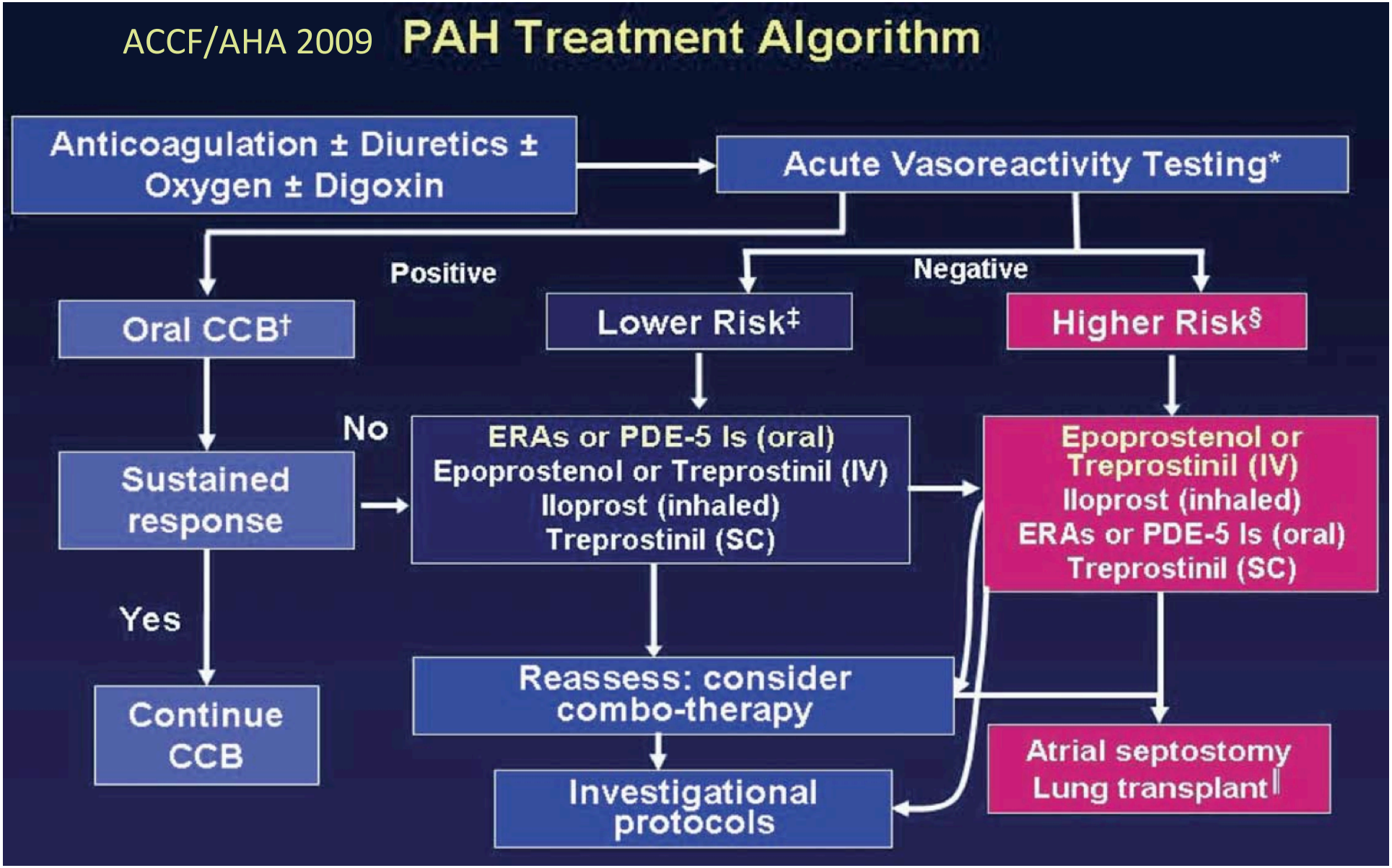
Conclusions

- Does not reduce all-cause mortality
- Reduces PAH worsening
  - NNT 8 for macitentan 10 mg/d vs placebo over 2.2 y
- Improves functional class
- Causes some adverse events
  - Headache (NNH 21)
  - Nasopharyngitis (NNH 28)
  - Bronchitis (NNH 17)
  - Anemia (NNH 10)



JACC 2009;53:1573-619

Macitentan's Role in PAH Therapy: My Take

- Note: Cost yet undetermined
  - Submitted to CDR in December 2013

- **PAH WHO class II-III:**
  - **1st line monotherapy agent**
    - Consider ahead of other endothelin-1 receptor antagonists & PDE-5 inhibitors
    - Start with 10 mg/d, decrease to 3 mg/d if not tolerated
  - Adjunct to prostanoid or PDE-5 inhibitor

- PAH WHO class IV:
  - Consider as adjunct to prostanoid

QUESTIONS?

Comparison Table

	Prostanoids	Other ET-1R Antagonists	PDE-5 Inhibitors	Macitentan
Efficacy	↓ mortality (epoprostenol ↑ function	↑ function	↑ function	↓ PAH worsening ↑ function
Adverse effects	• Headache • Jaw pain • Nausea • Diarrhea • Peripheral edema	• Anemia • Transaminitis • Hepatotoxicity	• Headache • Visual disturbance • Dyspepsia • Flushing • Limb pain	• Headache • Nasopharyngitis • Bronchitis • Anemia
Adherence	From 6-9 puffs daily to CIVI	PO once to twice daily	PO once to thrice daily	PO once daily
Cost per year	~35-100k	~55k	13k	?

JACC 2009;53:1573-619
NEJM 2005;353:2148-57
Respir Res 2010;11:12