Pulmonary Hypertension Medication Update

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No relevant disclosures

Objectives

- Describe the unique pharmacology for most recently approved pulmonary arterial hypertension (PAH) treatments
- Identify recent developments in the delivery of parenteral prostacyclin therapies
- Evaluate strategies for implementation of new, and/or escalation of existing, PAH therapies

Pulmonary Arterial Hypertension

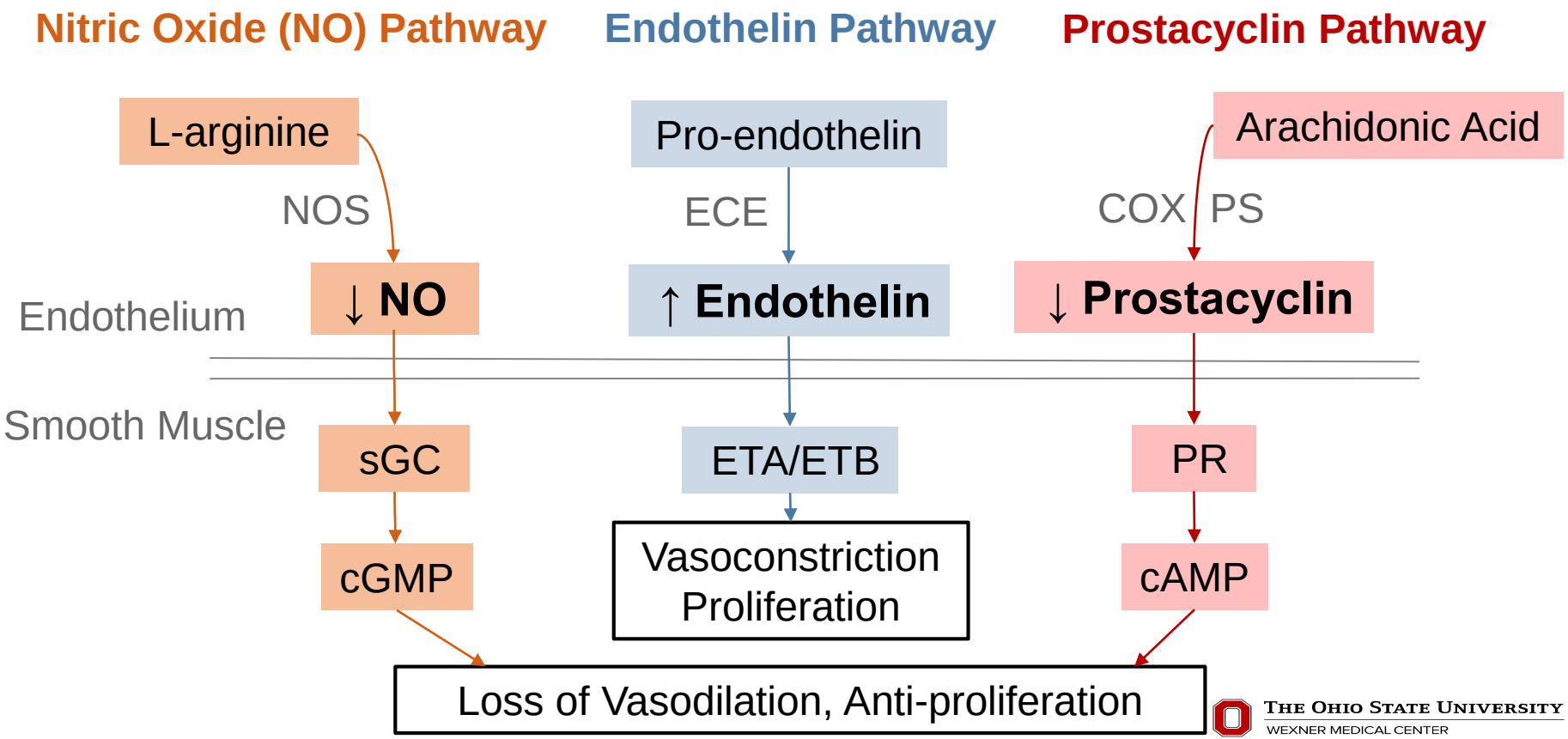
Hemodynamic Criteria:

- Mean Pulmonary Artery Pressure $\geq$ 25 mmHg
- Pulmonary Capillary Wedge Pressure $\leq$ 15 mmHg
- Pulmonary Vascular Resistance > 3 Wood units

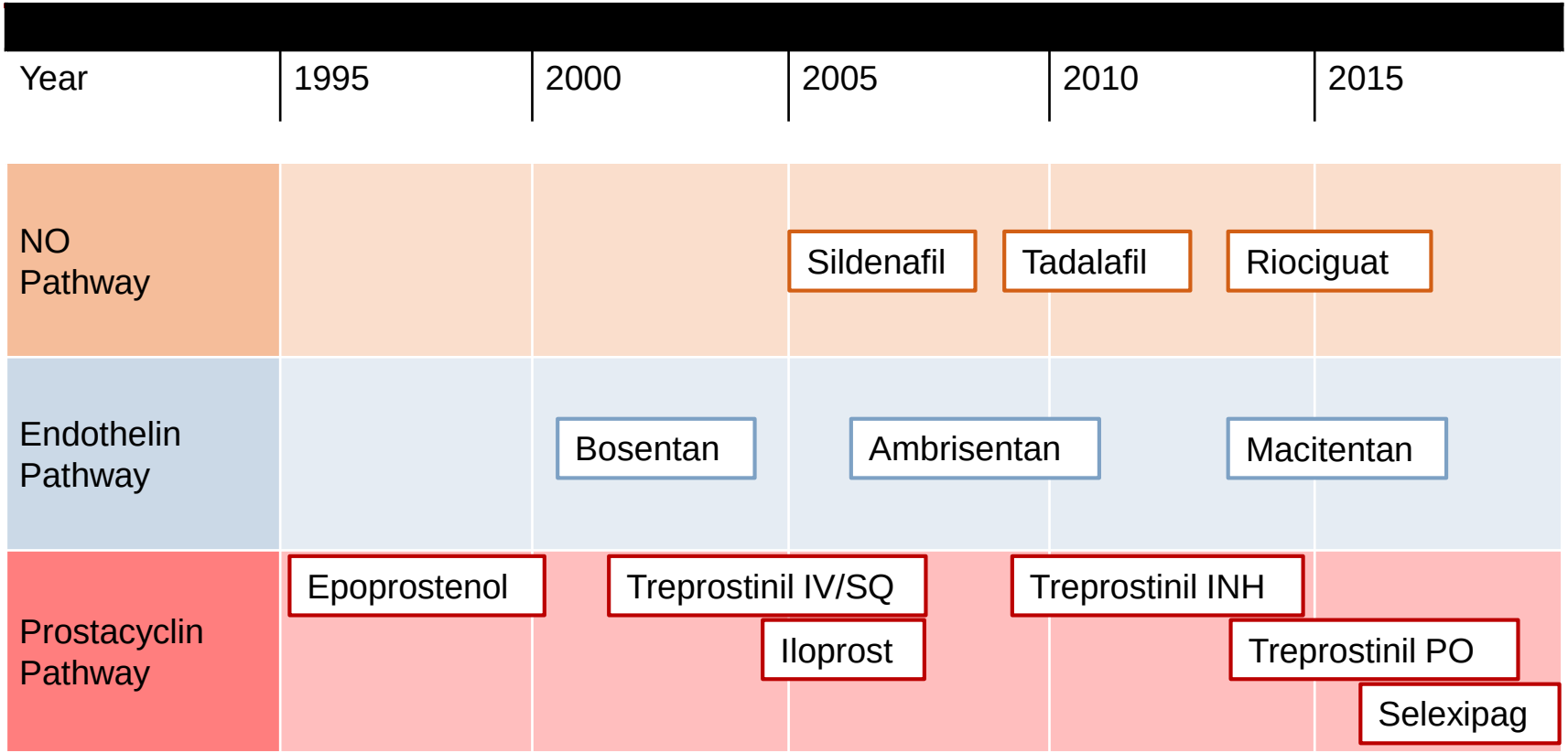
World Health Organization (WHO) Group I:

- 1.1 Idiopathic
- 1.2 Heritable
- 1.3 Drug and toxin induced
- 1.4 Associated with connective tissue disease, HIV, portal hypertension, CHD

PAH Therapy Targets

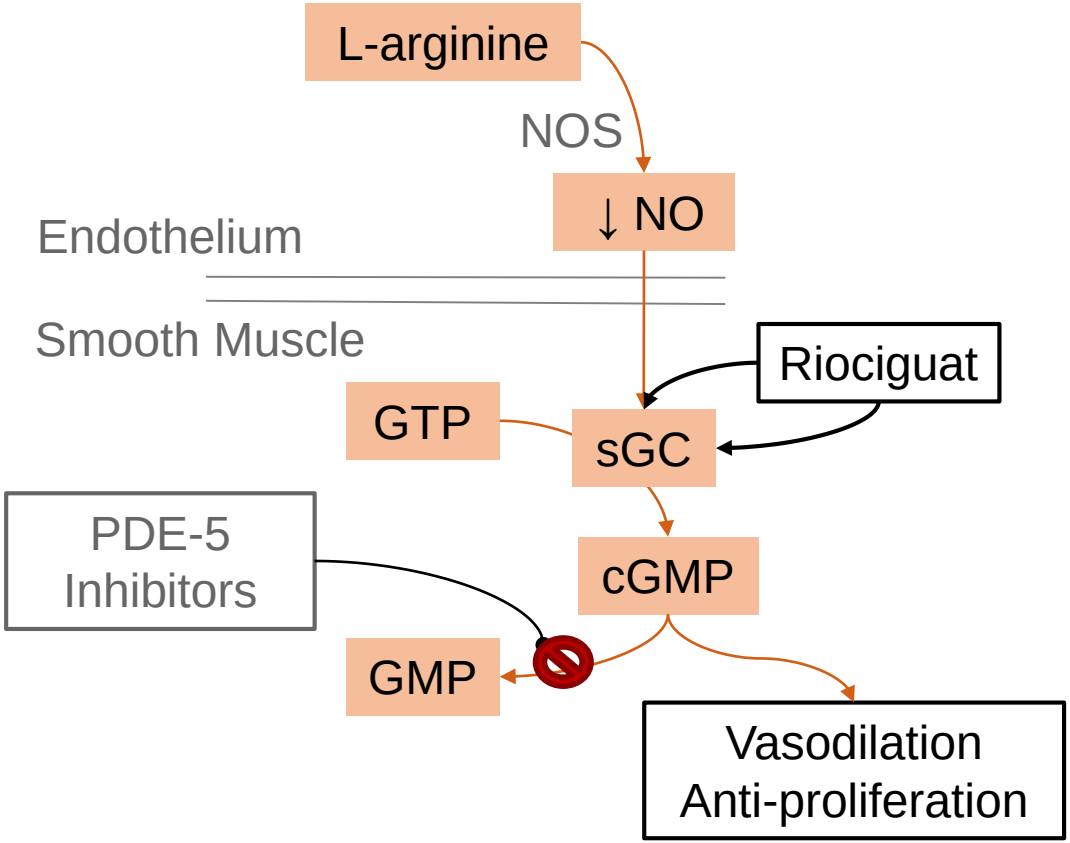


PAH Therapy FDA Approval Timeline



FDA.gov

Riociguat



Soluble guanylate cyclase stimulator

Nitric oxide-dependent and Nitric oxide-independent mechanisms

Riociguat – PATENT Trial

	Population	Treatment	Endpoints
PATENT (n = 443)	Group 1 PAH WHO II (42%) WHO III (53 %) Background ERA (44%)	**Riociguat** **Initial: 1 mg TID** **Titrated: 0.5-2.5 mg TID**	Duration: 12 weeks 1°: 6-MWD 2°: WHO functional class, clinical worsening
		Placebo	

6-MWD: 6-minute walk distance, ERA: endothelin receptor antagonist

Ghofrani, et al. *N Engl J Med* 2013;369:330-340

Riociguat – PATENT Trial

	Results	Selected Adverse Events
PATENT (n = 443)	1°: 6-MWD: +36m (p < 0.001) 2°: WHO Class Improvement: 21% vs. 14% (p = 0.003) Clinical worsening: 1% vs. 6% (p < 0.005)	Headache: 27% vs 20% Dyspepsia: 19% vs. 8% Hypotension: 10% vs. 2% Anemia: 8% vs. 2%

6-MWD: 6-minute walk distance
Clinical Worsening: Death, Transplant, Atrial Septostomy, Hospitalization, New PAH therapy, persistent worsening of WHO Class

- Sustained benefits in 6-MWD, WHO Class at 1 year follow-up demonstrated in PATENT-2 extension study

Ghofrani, et al. *N Engl J Med* 2013;369:330-340
Rubin L, et al. *Eur Respir J* 2015;0:1-11

sGC Stimulation vs PDE-5 Inhibition?

No randomized, controlled comparisons exist

RESPITE Trial

- Design: 24-week, open-label, uncontrolled analysis
- Population: 61 patients
  - WHO FC III, limited 6-MWD despite PDE-5 inhibitor treatment
- All converted to riociguat
- Results:
  - Improved 6-MWD (+31m)
  - WHO FC improved in 54% of patients
- Randomized follow-up study in progress

Hoeper M, et al. *Eur Resp J* 2017;50:1602425

Riociguat – Treatment Considerations

- **Indications:**
  - WHO Group 1
  - WHO Group 4 (CTEPH)
- **Dosing:**
  - Initial: 1 mg three times daily
  - Titrated every 2 weeks
  - Maximum 2.5 mg three times daily
- **Adjustments**
  - Renal – None
  - Hepatic – No data for severe hepatic impairment
- **Drug Interactions:**
  - ***Contraindicated****:*
    - PDE-5 inhibitors
    - Nitrates
  - Strong 3A4/P-gp inhibitors:
    - Initial 0.5 mg TID
  - Strong 3A4/P-gp inducers, smoking:
    - Doses > 2.5 mg may be used
- **Teratogenic**
  - *REMS enrollment required*, avoid use in pregnancy

Nitric Oxide Pathway Summary

	Riociguat	Sildenafil	Tadalafil
Mechanism	sGC Stimulator	PDE5 inhibitor	PDE5 inhibitor
Dosing	0.5-2.5 mg TID	20 mg TID	40 mg daily
Trials	PATENT	SUPER	PHIRST
Benefits	6-MWD WHO FC Clinical worsening	6-MWD WHO FC	6-MWD Clinical worsening
Selected ADEs	Hypotension Anemia Dyspepsia	Flushing Diarrhea	Flushing Myalgia
REMS	Yes	No	No
Cost Considerations	Brand only	Generic available	Generic approved

Ghofrani, et al. *N Engl J Med* 2013;369:330-340; Galie, et al. *N Engl J Med* 2005; 353:2148-57
Galie, et al. *Circulation* 2009;119:2894-2903

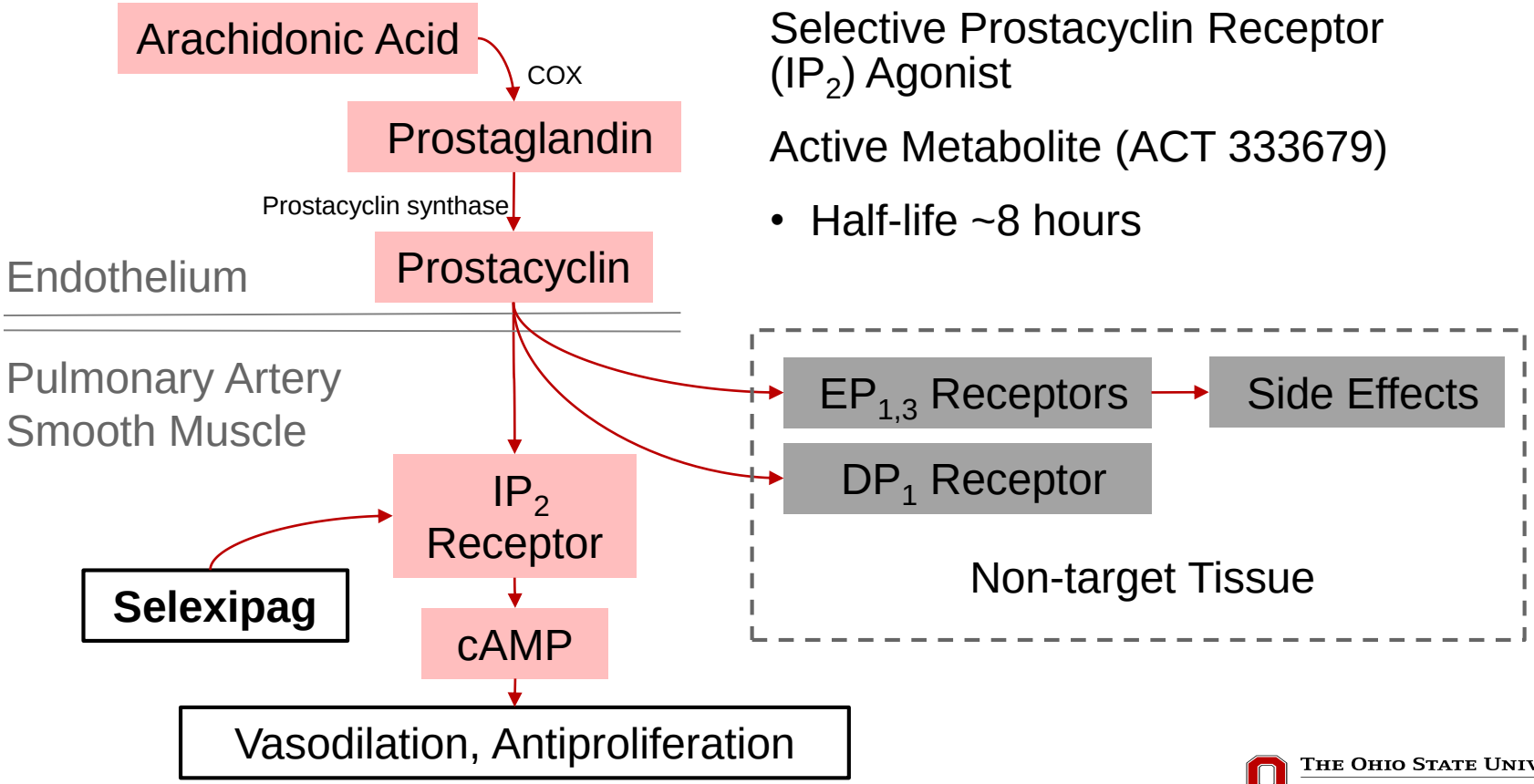
Endothelin Receptor Antagonists

	Bosentan	Ambrisentan	Macitentan
Mechanism	ETA & ETB	ETA only	ETA & ETB
Dosing	62.5-125 mg BID	5-10 mg daily	10 mg daily
Trials	BREATHE	ARIES	SERAPHIN
Benefits	6MWD TTCW	6MWD WHO FC TTCW	6MWD WHO FC TTCW
Selected ADEs	Elevated LFTs Flushing	Peripheral edema Congestion/Sinusitis	Nasopharyngitis Anemia
REMS	Yes – Pregnancy and LFTs	Yes - Pregnancy	Yes - Pregnancy

TTCW: Time to clinical worsening (Death, lung transplant, hospitalization, lack of improvement/worsening necessitating alternative therapy)

Rubin, et al. *N Engl J Med* 2002;346:896-903; Galie, et al. *Circulation* 2008;117:3010-19
Pulido, et al. *N Engl J Med* 2013;369:809-18

Selexipag



Selective Prostacyclin Receptor (IP_2) Agonist

Active Metabolite (ACT 333679)

- Half-life ~8 hours

Selexipag - GRIPHON Trial

	Population	Treatment	Endpoints
GRIPHON (n = 1156)	Group 1 PAH WHO II (46%) WHO III (53 %) Tx naïve (20%) Prior PDE-5 (15%) Prior ERA (32%) Both (32%)	**Selexipag** **Initial: 200 mcg BID** **Titrated: 200-1600 mcg BID**	Duration ~ 67 weeks 1°: Death or PAH complication 2°: Change in 6-MWD
		Placebo	

PAH Complication: disease progression/worsening resulting in hospitalization, need for parenteral prostanoid, oxygen or end-stage treatment (transplant, atrial septostomy)
6-MWD: 6-minute walk distance

Sitbon, et al. *N Engl J Med* 2015;373(16):2522-2533

Selexipag - GRIPHON Trial

	Results	Selected Adverse Effects
GRIPHON (n = 1156)	1°: Death or PAH Complication: 27.0% vs 41.6% HR 0.60 (0.46-0.78), p < 0.001 2°: Change in 6-MWD: +12 m (1 to 24, p=0.003)	Headache: 65% vs 33% Diarrhea: 42% vs 19% Nausea: 34% vs 19% Jaw Pain: 26% vs 6% Myalgia: 16% vs 6% (p<0.001 for all)

PAH Complication: disease progression/worsening resulting in hospitalization, need for parenteral prostanoid, oxygen or end-stage treatment (transplant, atrial septostomy)
6-MWD: 6-minute walk distance

Sitbon, et al. *N Engl J Med* 2015;373(16):2522-2533

Oral Prostacyclin Therapy – Adverse Effects

	GRIPHON		FREEDOM-C2	
	Placebo	**Selexipag**	**Treprostinil**	Placebo
Headache	32%	**65%**	**71%**	40%
Diarrhea	19%	**42%**	**55%**	25%
Nausea	19%	**34%**	**46%**	22%
Vomiting	9%	**18%**	**21%**	10%
Jaw Pain	6%	**26%**	**25%**	7%
Flushing	5%	**12%**	**35%**	10%

Sitbon, et al. *N Engl J Med* 2015;373(16):2522-2533
Tapson, et al. *Chest* 2013;144(3):952-58

Selexipag – Treatment Considerations

Indications:

- WHO Group 1

Dosing:

- Initial: 200 mcg twice daily
- Titrate weekly by 200 mcg twice daily
- Max 1600 mcg twice daily

Interruption in therapy

- If missed 3 or more days, resume at lower dose, re-titrate

A**djustments**

- Renal – None
- Hepatic
  - Moderate: Reduce initial and titration increment to 200 mcg daily
  - Severe: Avoid use

Drug Interactions

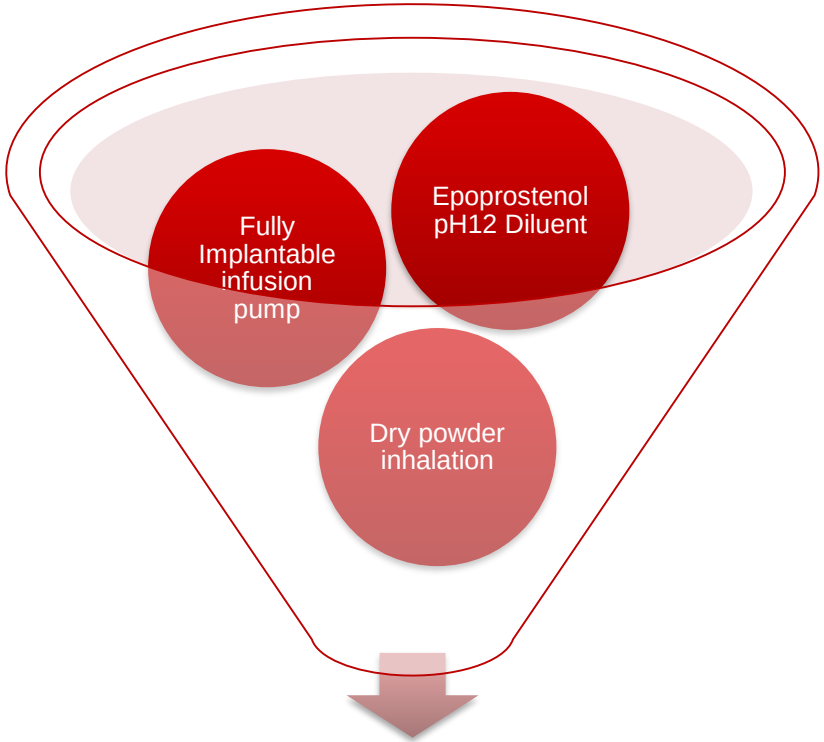
- Strong CYP 2C8 inhibitors(ex. Gemfibrozil)
  - Avoid use
- Strong CYP 2C8 inducers (ex. Rifampin)
  - Higher doses may be used

Oral Prostacyclin Pathway Summary

	Selexipag	Oral Treprostinil
Mechanism	Selective IP Receptor Agonist	Prostanoid
Dosing Frequency	Twice daily	**Three times daily** (also labeled for twice daily)
Trials	GRIPHON	FREEDOM Series
Benefits	PAH Complication 6-MWD	*Monotherapy:* - 6-MWD *Combination Therapy:* - None
Selected ADEs	Headache N/V/D	Headache N/V/D
Interactions	CYP2C8	CYP2C8
Pill burden?	Minimal (2 tab/day)	Possibly

Sitbon, et al. *N Engl J Med* 2015;373(16):2522-2533; Tapson, et al. *Chest* 2013;144(3):952-58
Jing, et al. *Circulation* 2013;127:624-33

Parenteral Prostacyclin Administration Enhancements



Parenteral Prostacyclin Summary

	Epoprostenol (IV)	Treprostinil (IV)	Treprostinil (SQ)
Half-life	**Minutes**	Hours	Hours
Hepatic Metabolism?	No	Yes	Yes
Room Temp Stability	***Yes***	Yes	Yes
Intravascular Access?	Yes	Yes	**No**
External pump?	Yes	Yes/***No (late 2019)***	Yes
Site Pain?	No	No	**Yes**

Inhaled Prostacyclin Summary

	Treprostinil	Iloprost
Dose	18-54 mcg (3-9 breaths) *- Long treatment time*	2.5-5 mcg
Dosing Frequency	4 times daily	**6-9 times daily** *- Frequent administration*
Specialized nebulizer	Yes	Yes
Compatible with ventilator?	No	No

So many options, so little time

WHO Group I PAH

↓

Negative Vasoreactivity

↓

Risk Stratification

High Risk → IV Prostacyclin

Low/Mod Risk → Oral Monotherapy or Combination Therapy

Measure/treatment	Class[a]-Level[b] WHO-FC II		WHO-FC III	
Calcium channel blockers	I	C[d]	I	C[d]
Endothelin receptor antagonists	I	A	I	A
Ambrisentan	I	A	I	A
Phosphodiesterase type 5 inhibitors	I	B	I	B
Macitentan added to sildenafil[d]	I	B	I	B
Riociguat added to bosentan	IIb	B	IIb	B
Guanylate cyclase stimulators	I	B	I	B
Prostacyclin analogues	-	-	I	A
Selexipag[e] added to ERA and/or PDE-5i[d]	-	-	I	B
Sildenafil added to epoprostenol	-	-	IIa	C
Treprostinil inhaled added to sildenafil or bosentan	-	-	I	B
Iloprost inhaled added to bosentan	-	-	I	B
Tadalafil added to bosentan	-	-	IIa	C
Ambrisentan added to sildenafil	-	-	IIb	B
Bosentan added to epoprostenol	-	-	IIb	B
Bosentan added to sildenafil	I	B	I	B
Sildenafil added to bosentan	IIa	B	IIa	B
Other double combinations	IIa	C	IIa	C
Other triple combinations	IIb	B	IIb	B
	IIb	C	IIb	C
	IIb	C	IIb	C
	IIb	C	IIb	C
	IIb	C	IIb	C

Measure/treatment	Class[a]-Level[b] WHO-FC II		WHO-FC III	
Ambrisentan + tadalafil[d]	I	B	I	B
Other ERA + PDE-5i	IIa	C	IIa	C
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C
Bosentan + i.v. epoprostenol	-	-	IIa	C
Other ERA or PDE-5i + s.c. treprostinil			IIb	C
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C

Galie N, et al. *Eur Heart J* 2016;37:67-119

Sequential Combination Therapy (Example)

	Step 1	Step 2	Step 3	Step 4
NO Pathway	Sildenafil	Sildenafil +	Sildenafil +	Sildenafil +
Endothelin Pathway		Bosentan	Bosentan +	Bosentan +
Prostacyclin Pathway			Inhaled Treprostinil	IV Epoprostenol
Supportive	>> Diuretics/Oxygen/Anticoagulation >>			

PAH Therapy – Upfront Combination – AMBITION Trial

	Population	Treatment	Endpoints
AMBITION (n = 500)	Treatment naïve Group 1 PAH WHO FC II (31%) WHO FC III (69 %)	Ambrisentan 10 mg + Placebo	Follow Up ~ 1.5 years 1°: Time to Clinical Failure 2°: (at 24 weeks) • 6-MWD • WHO Functional Class
		Ambrisentan 10 mg + Tadalafil 40 mg	
		Tadalafil 40 mg + Placebo	

Clinical Failure: Composite of death, hospitalization for PAH, disease progression, unsatisfactory response
6-MWD: 6-minute walk distance

Galie, N, et al. *N Engl J Med* 2015;373:834-44

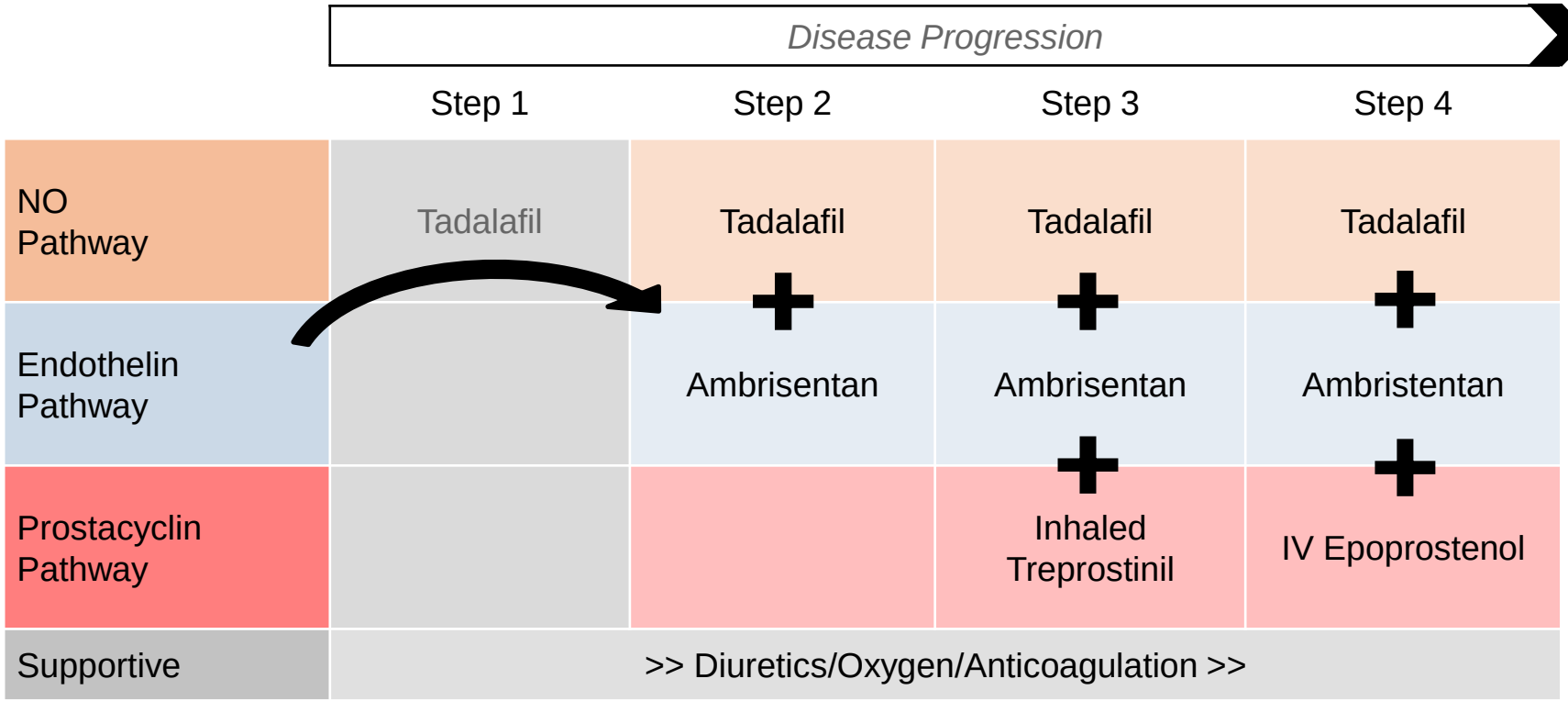
PAH Therapy – Upfront Combination – AMBITION Trial

Results				Selected Adverse Events
	Incidence of Clinical Failure	6-MWD	WHO FC Change	More common in combination treatment: • Peripheral edema • Headache • Nasal congestion • Anemia
Ambrisentan + Placebo	34%	+27 m		
Ambrisentan + Tadalafil	**18%***	**+49 m***	**No difference**	
Tadalafil + Placebo	28%	+23 m		

Clinical Failure: Composite of death, hospitalization for PAH, disease progression, unsatisfactory response
6MWD: 6-minute walk distance
*p< 0.05

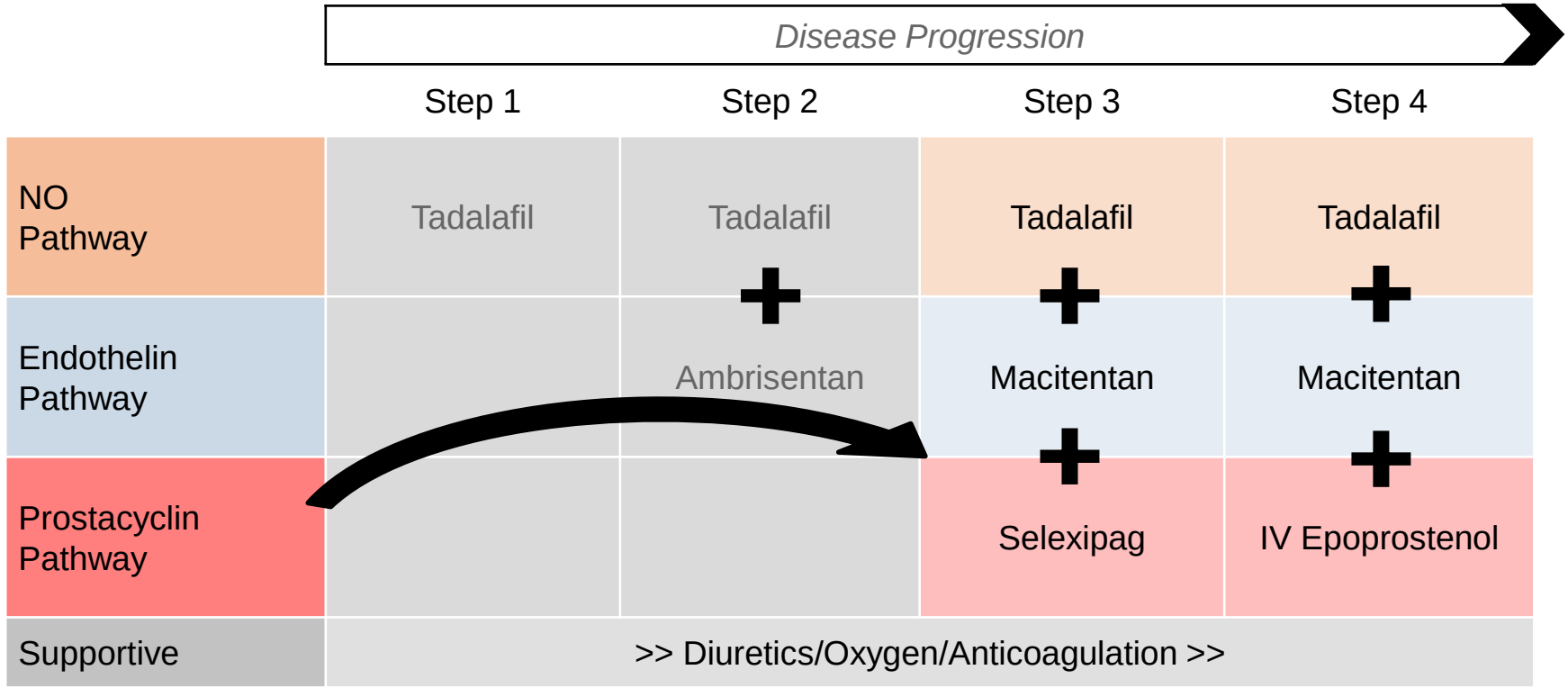
Galie, N, et al. *N Engl J Med* 2015;373:834-44

PAH Therapy - Upfront Dual Combination



Galie, N, et al. *N Engl J Med* 2015;373:834-44

Upfront Triple Combination? TBD – *Under investigation*



ClinicalTrials.gov NCT02558231; Sitbon O. et al, *Eur Respir J* 2014;43:1691-1697

PAH Therapy – Treatment Goal = Low Risk Profile

Risk Group (Est. 1-yr Mortality)	Low Risk (<5%)	Moderate Risk (5-10%)	High Risk (>10%)
WHO FC (progression)	I, II (no)	III (slow)	IV (rapid)
6-MWD (m)	>440	165-440	<165
Syncope?	No	Occasional	Repeated
Pericardial Effusion?	No	Minimal if any	Yes
Hemodynamics	RAP < 8 CI 2.5 or more	RAP 8-14 CI 2.0-2.4	RAP > 14 CI < 2

Abbreviated version of 2015 ESC Guideline Criteria (additional criteria include CPET parameters, BNP/NT-proBNP, others)
6MWD: 6-minute walk distance; RAP: Right Atrial Pressure, CI: Cardiac index

Galie N, et al. *Eur Heart J* 2016;37:67-119

Summary

- Current PAH therapies target 3 pathways: Nitric Oxide, Endothelin, and Prostacyclin
- New agents, particularly riociguat and selexipag possess unique pharmacology and may offer advantages over existing therapies
- Advances in the delivery of parenteral prostacyclin therapy may improve patient experience
- Upfront combination therapy may offer advantages over monotherapy/sequential combination therapy
- Regardless of agent(s) used, patients should be treated with a goal of achieving a low risk profile

Thank You

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