Update on New Cardiac & Respiratory Medications with an Emphasis on Pulmonary Hypertension and Pulmonary fibrosis

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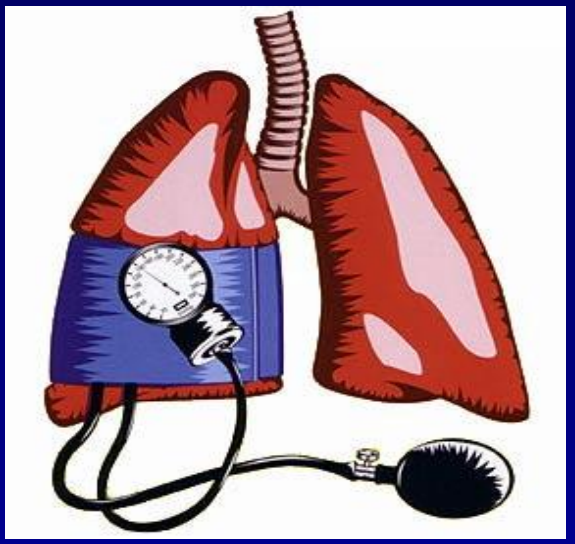
Objectives



- Review the Epidemiology and pathophysiology of Pulmonary arterial Hypertension (PAH) and Pulmonary Fibrosis
- Review the Signs/ Symptoms & Treatment Options of PAH and Pulmonary Fibrosis
- Learn about Some Newly Approved Cardiac and Respiratory Medications and Their Role in Patient Care

Epidemiology of PAH

- Hospitalization: ~200,000 annually in the U.S
- Mean age of diagnosis: 45 years
- Occurs in women twice as frequently as men
- Historically: Due to rapid progression of morbidity and mortality, once patients were diagnosed with pulmonary hypertension they were described as entering "the kingdom of the near-dead"
- Modern day: Patient survival has dramatically improved as treatment options for PAH have increased

McGoon, et al. *J Am Coll Cardiol.* 2013;62(25):S51-9.

The Expansion of Treatment Options for PAH

18 years ago
- No treatments for PAH

12 years ago
- 1 treatment for PAH

Today
- 12 treatment options for PAH

Pulmonary Hypertension Association, January 2014.

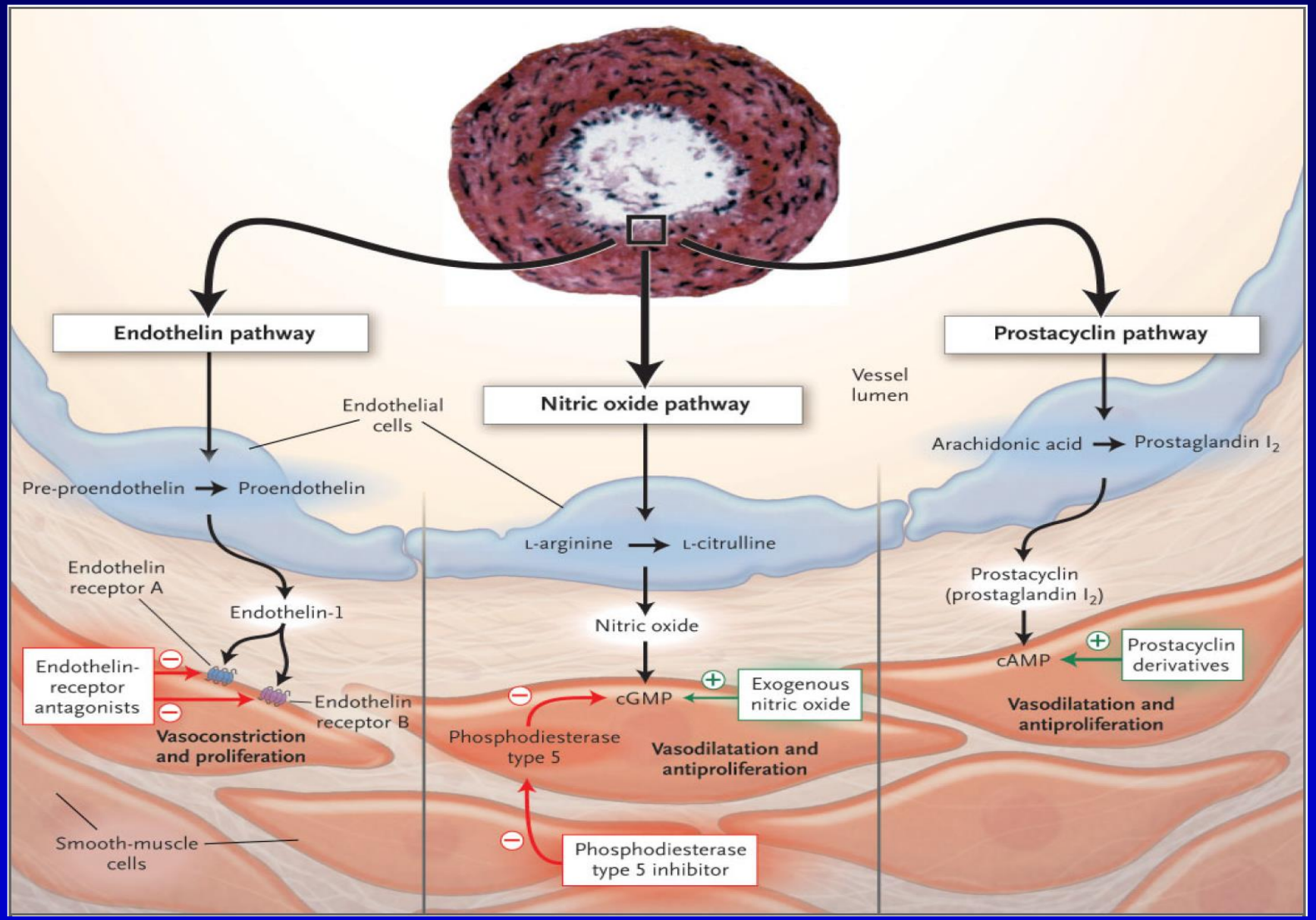
Pathology of Pulmonary Hypertension

Overview

- Pulmonary hypertension (PH) is an obstructive lung panvasculopathy
- Patient prognosis is primarily determined by the functional status of the right ventricle (RV)
- Most common cause of death is RV failure

Tuder, et al. *J Am Coll Cardiol.* 2013;62(25):S4-12.

Mechanisms of Pathology for PAH



NEJM 351;14 2004

Definition of Pulmonary Hypertension

- General definition
  - Mean PAP ≥ 25 mm Hg at rest, measured by right heart catheterization
- Hemodynamic characterization of PAH
  - Mean PAP ≥ 25 mm Hg, PAWP ≤ 15 mm Hg, elevated PVR (> 3 Wood Units)

PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance

WHO Functional Classification for PAH

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, fatigue, chest pain, or near syncope.
Class II	Slight limitation of physical activity; no discomfort at rest. Ordinary activity causes undue dyspnea, fatigue, chest pain, or near syncope.
Class III	Marked limitation of physical activity; no discomfort at rest. Less than ordinary physical activity causes undue dyspnea, fatigue, chest pain, or near syncope.
Class IV	Inability to perform any physical activity without symptoms; signs of right ventricular failure or syncope; dyspnea and / or fatigue may be present at rest; discomfort is increased by any physical activity.

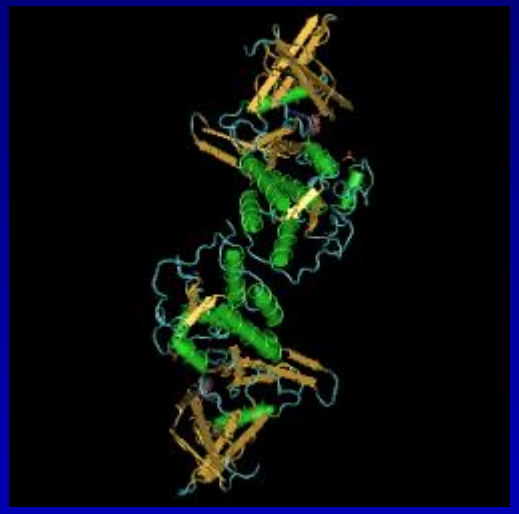
Taichman, et al. *Clin Chest Med*. 2007;28:1-22.

Drug- and Toxin-Induced PAH

Definite	• Aminorex • Fenfluramine • Dexfenfluramine	• Toxic rapeseed oil • Benfluorex • SSRIs
Likely	• Amphetamines • L-Tryptophan • Methamphetamines • Dasatinib	
Possible	• Cocaine • Phenylpropanolamine • St. John's wort	• Chemotherapeutic agents • Interferon α and β • Amphetamine-like drugs
Unlikely	• Oral contraceptives • Estrogen • Cigarette smoking	

Simonneau, et al. *J Am Coll Cardiol.* 2013;62(25):S34-41.

Genetic Mutations in PAH



- BMPR2
  - Major predisposing gene
  - Linked to vascular remodeling due to smooth muscle cell proliferation
  - Over 300 mutations have been identified
  - Found in >70% of patients with heritable PAH
  - Found in ≈ 20% of patients with idiopathic PAH
- ALK-1
  - Major gene when PAH is associated with hereditary hemorrhagic telanglectasia (HHT)
- Less common mutations:
  - Endoglin, SMAD9, Caveolin-1, KCNK3

Soubrier, et al. *J Am Coll Cardiol.* 2013;62(25):S13-21.

PAH Associated With HIV Infection

- Rate of occurrence of PAH = 0.5% of patients with HIV
- Associated with duration of the HIV and use of highly-active antiretroviral therapies (HAART)
- French registry: 5 year survival rate > 70%

Simonneau, et al. *J Am Coll Cardiol.* 2013;62(25):S34-41.

Signs/Symptoms

- Often vague in the beginning and may be attributed to asthma, lack of physical activity, or general fatigue.

Symptoms	Signs
Dyspnea on exertion	Jugular venous distention
Fatigue	Prominent right ventricular impulse
Syncope	Accentuated pulmonic valve component (P_2)
Anginal chest pain	Right-sided third heart sound (S_3)
Hemoptysis	Tricuspid insufficiency murmur
Raynaud's phenomenon	Heptomegaly
	Peripheral edema

Nauser, 2001.

Diagnosis

- A high index suspicion, meticulous history, and careful physical exam are paramount with particular attention paid to:
  - Previous medical conditions
  - Drug use
  - Family history
- ECG may demonstrate signs of right ventricular hypertrophy such as tall right precordial R waves, right axis deviation, and right ventricular strain.
- Chest radiograph may show evidence of underlying lung disease and prominent pulmonary arteries.

Nauser, 2001.

Diagnostic Issues

- Misdiagnosis[1]
  - Most patients see three or more physicians over a three-year period before an accurate diagnosis is made
- Diagnostic delay[1]
  - Time to reach diagnosis has not improved in 20 years
- Advanced disease at diagnosis[2]
  - Approximately 75% of patients have advanced disease at diagnosis (functional class III and IV)

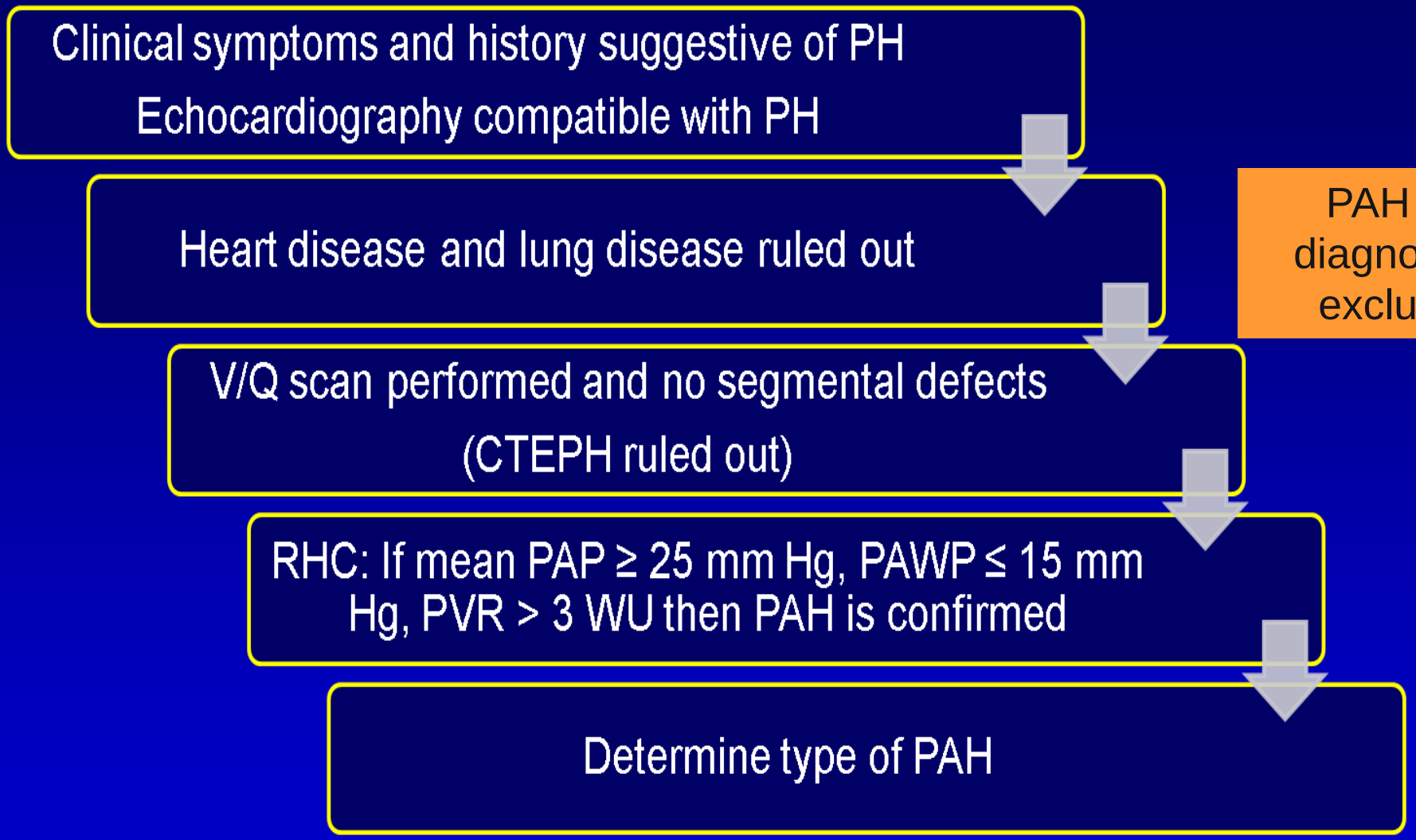
1) Deano, et al. *JAMA Intern Med*. 2013;173(10):887-93. 2) Thenappan, et al. *Eur Respir J*. 2007;30(6):1103-10.

Evaluation of RV Function: Echocardiography

- Most common method used in clinical practice to evaluate the RV
- Used in patient monitoring to:
  - Assess the RV
  - Evaluate RV size and function
  - Determine cardiac performance impairment
  - Measure right atrial size
  - Assess pericardial effusion

Agarwal, et al. *Am Heart J*. 2011;162:201-13.

Diagnostic Algorithm for PAH



PAH is a diagnosis of exclusion

Hoeper, et al. *J Am Coll Cardiol.* 2013;62(25):S42-50.

V/Q = ventilation / perfusion lung scan; CTEPH = chronic thromboembolic pulmonary hypertension; RHC = right heart catheterization; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; WU = wood units

Advance Therapy Treatment of PAH

General Measures and Supportive Therapy

General Measures

- Rehabilitation / Exercise
  - Recommended after stabilized and on therapy
  - Requires close supervision by an experienced PAH care center
  - Optimal method, duration, and intensity of activity are unknown
- Psychosocial support
- Family planning
  - Pregnancy is associated with a considerable mortality rate in patients with PAH, and oral contraceptives are not contraindicated
- Vaccinations
  - Influenza and pneumococcal immunization

Galie, et al. *J Am Coll Cardiol.* 2013;62(25):S60-72.

General Measures and Supportive Therapy

Supportive Therapy

- Anticoagulants
- Diuretics
- Oxygen
- Digoxin

Galie, et al. *J Am Coll Cardiol.* 2013;62(25):S60-72.

General Measures and Supportive Therapy

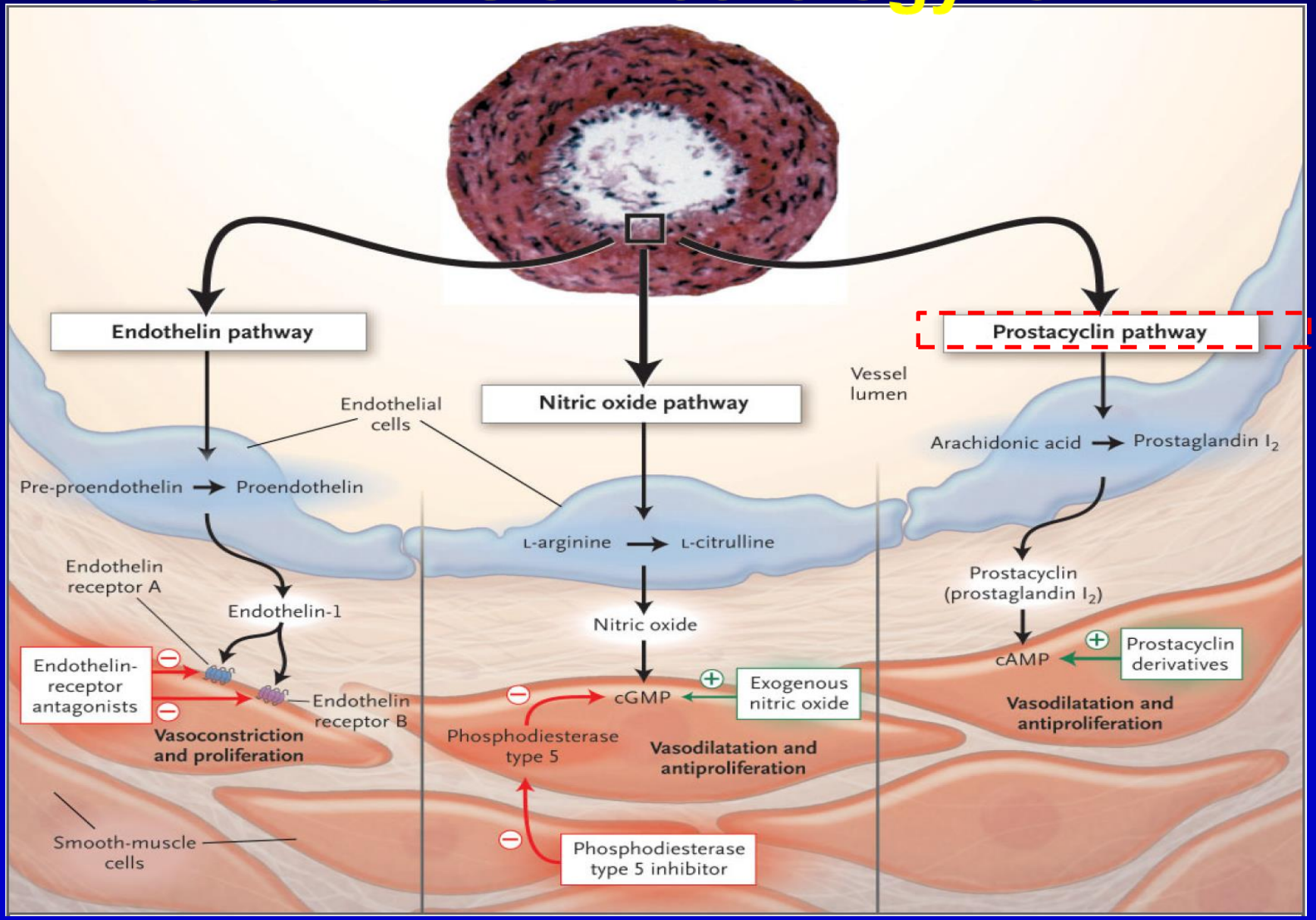
Chronic Calcium Channel Blocker Therapy

- Responders
  - Patients with a positive response to acute vasoreactivity testing
  - Positive response = reduction of mean PAP ≥ 10 mm Hg to reach a mean PAP ≤ 40 mm Hg with a normalized or increased cardiac output
  - < 10% of patients with idiopathic PAH
- Avoid verapamil due to negative inotropic effects
- Therapeutics

Amlodipine	**20 – 30 mg/day**
Nifedipine	**180 – 240 mg/day**
Diltiazem	**720 – 960 mg/day**

Agarwal, et al. *Am Heart J*. 2011;162:201-13. Galie, et al. *J Am Coll Cardiol.* 2013;62(25):S60-72.

Mechanisms of Pathology for PAH



Prostacyclin Pathway

- Prostacyclin
  - Produced primarily by endothelial cells
  - Induces potent vasodilation of vascular beds
  - Inhibits platelet aggregation
  - Improves cardiac contractility
  - Cytoprotective and antiproliferative properties
- Prostacyclin analogs

Epoprostenol	**Continuous IV infusion, inhalation**
Iloprost	**Inhalation**
Treprostinil	**Subcutaneous, IV, inhalation, oral**

Galie, et al. *J Am Coll Cardiol.* 2013;62(25):S60-72.

Treatment

Prostanoids

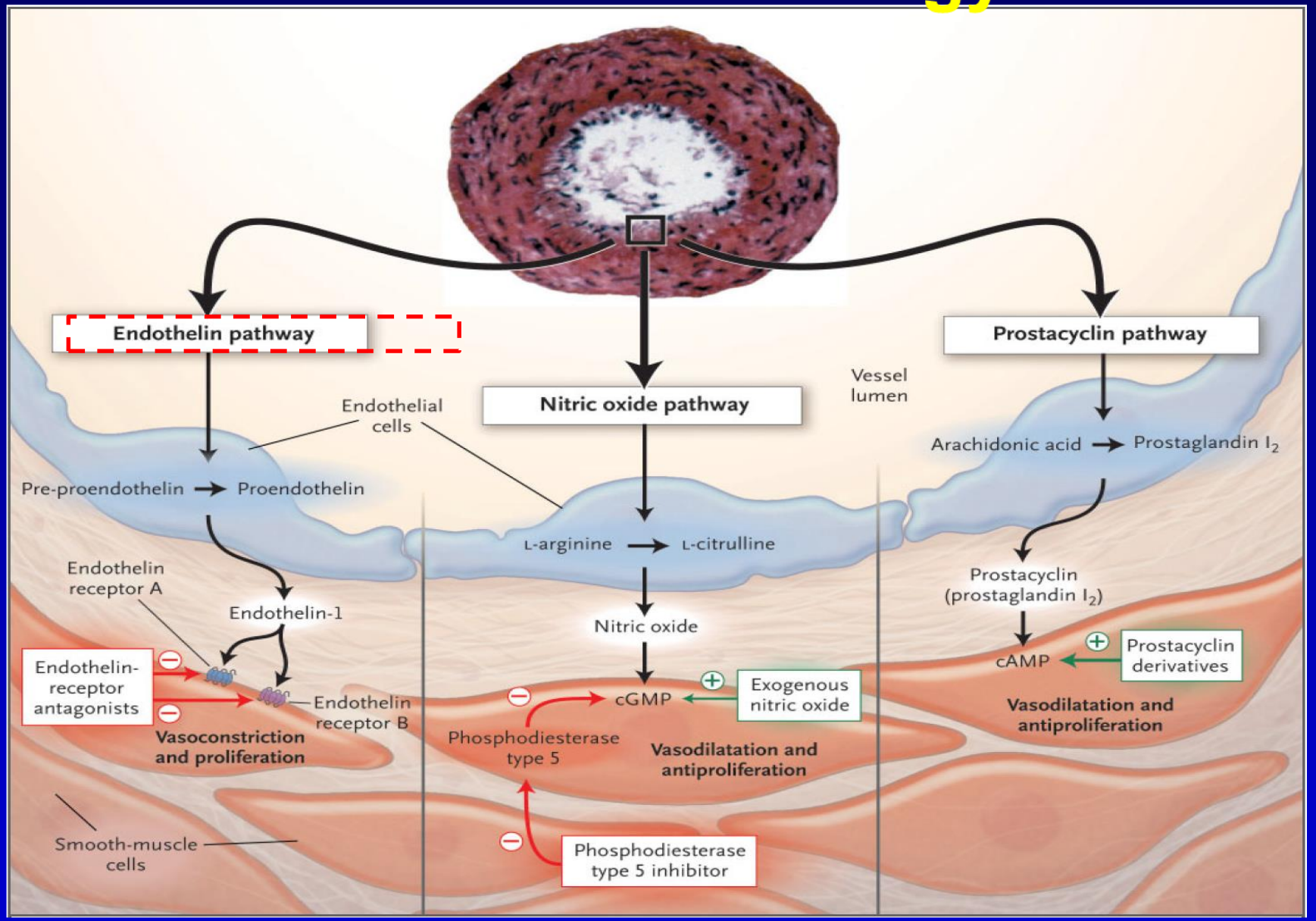
DIRECT VASODILATION AND INHIBITION OF PLATELET AGGREGATION

Generic	Brand	Route	Dose
Epoprostenol	Flolan/Velenti	IV continuous	2 ng/kg/min titrated up to dose effect or tolerance
Treprostinil	Remodulin Tyvaso Orenitram	IV/SQ Inhalation Oral	1.25 ng/kg/min x4 weeks then increase to 2.5 ng/kg/min 18-54 mcg 4 times daily 0.25 mg Q12H, titrate as tolerated
Iloprost	Ventavis	Inhalation	2.5-5 mcg per dose 6-9 times daily

- Side effects: flushing, headache, hypotension, nausea, tachycardia, increased cough (iloprost)
- Continuous IV infusions of Flolan and Remodulin carry a risk of infection and catheter obstruction. Subcutaneous infusion of Remodulin is preferred

Badesch, 2007

Mechanisms of Pathology for PAH



Endothelin Pathway

- Endothelin
  - Plasma levels are elevated in patients with PAH
  - Increases vasoconstriction
  - Mitogenic properties
- Endothelin receptor antagonists

Bosentan	**Oral**
Ambrisentan	**Oral**
Macitentan	**Oral**

Galie, et al. *J Am Coll Cardiol.* 2013;62(25):S60-72.

Treatment

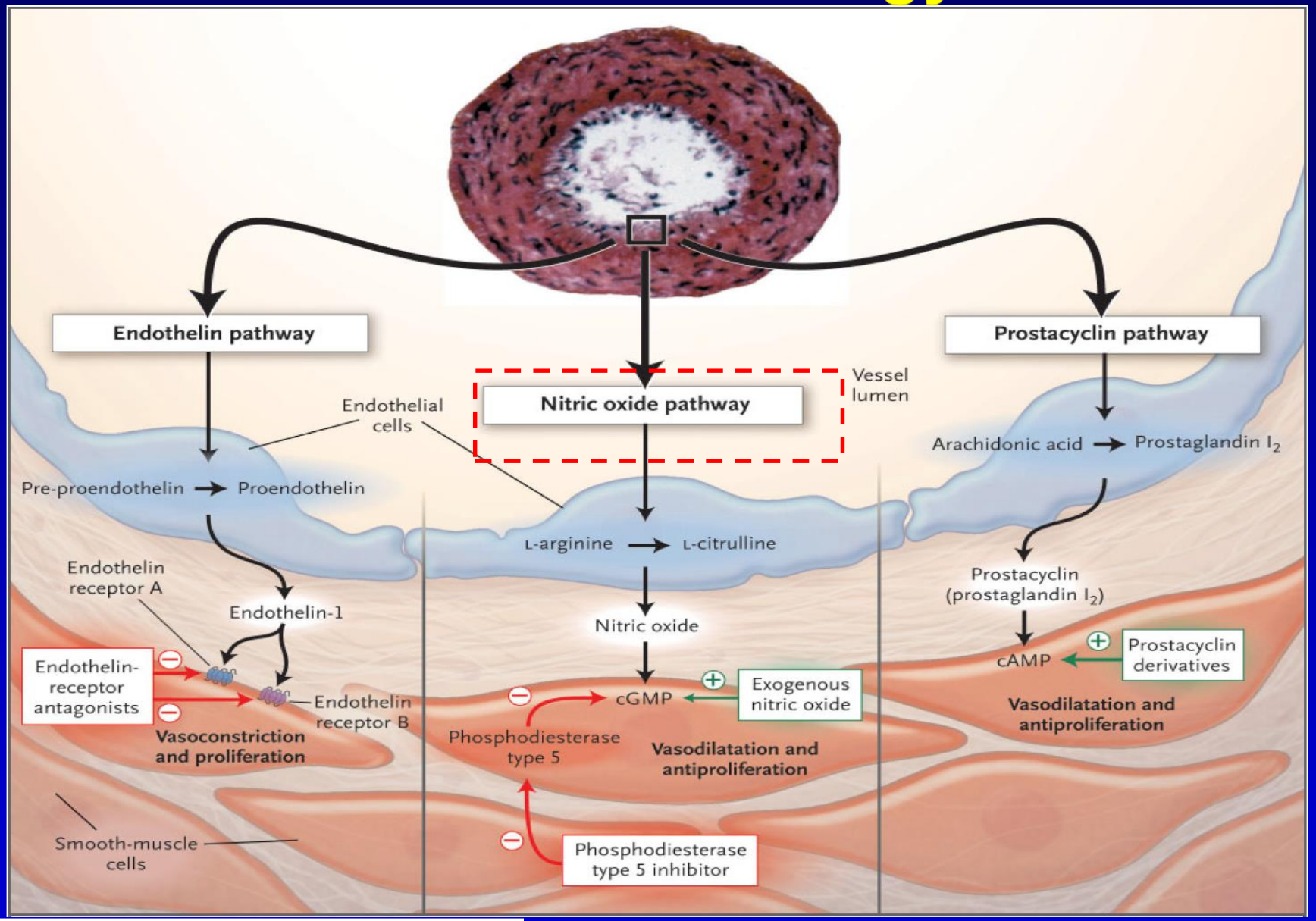
Endothelian Antagonists

Generic	Brand	Dose	REMS	BBW
Bosentan	Tracleer	125 mg BID	TAP	Hepatotoxicity Teratogenicity
Ambrisentan	Letairis	5-10 mg daily	LEAP	Pregnancy
Macitentan	Opsumit	10mg daily	OpsumitREMS	Embryo-fetal toxicity

- Side effects: Peripheral edema, transient anemia, possible decreased sperm count
- Female patients must me on reliable contraception during treatment and one month after treatment is stopped
- Indication – functional class II, III, and IV

Badesch, 2007

Mechanisms of Pathology for PAH



N ENGL J MED 351;14 WWW.NEJM.ORG SEPTEMBER 30, 2004

Treatment

Phosphodiesterase inhibitors

Inhibits cGMP-specific PDE5 in the smooth muscle of the pulmonary vasculature leading to increased nitric oxide and vasodilation

Generic	Brand	Dose
Sildenafil	Revatio	20mg PO TID
Tadalafil	Adcirca	40mg PO daily

- Side effects: flushing, headache, hypotension,
  - Sildenafil: dyspepsia, visual disturbances, epistaxis
  - Tadalafil: myalgia, nasopharyngitis, nausea, back pain

- Indication – functional class II, III, IV

Badesch, 2007

Riociguat for PAH

- Soluble guanylate cyclase stimulator – targets the nitric oxide pathway
- Indication – PAH and CTEPH (FCII, III, and IV)
- Administration – oral
- Dosage = 1 mg – 2.5 mg three times daily

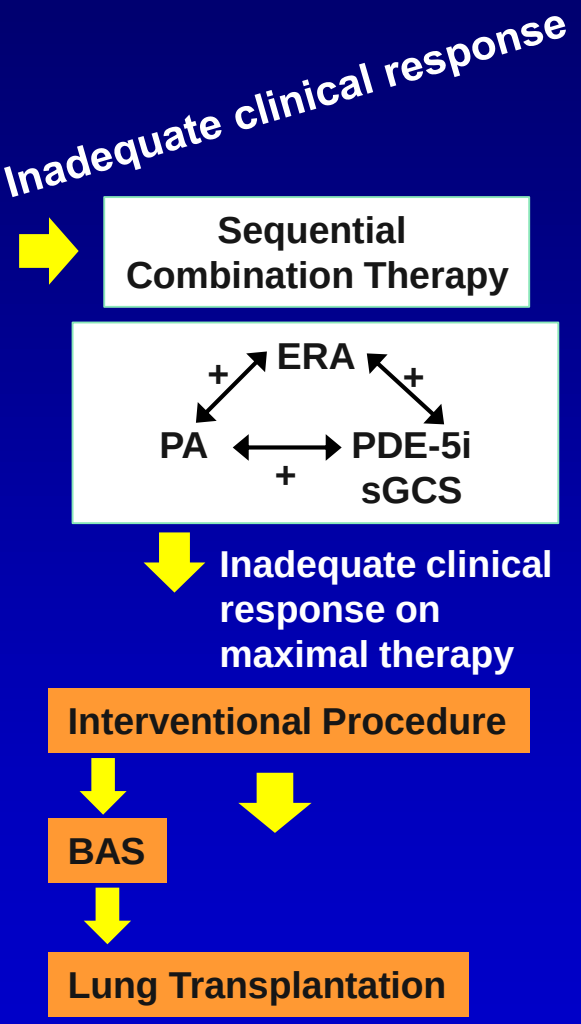
Early Initiation of Combination Therapy for PAH

- Combination therapy used in early PAH disease
- Debated by clinicians and researchers
- May improve patient outcomes
- May prevent or slow disease progression
- May reduce costs associated with managing clinical worsening
- Well-controlled studies are needed to test this practice

Affuso, et al. *World J Cardiol*. 2010;2(3):68-70.

Evidence-Based Treatment Algorithm

	WHO FC II	WHO FC III	WHO FC IV
IA/B	Bosentan Ambrisentan Macitentan Sildenafil Tadalafil Riociguat	Bosentan Ambrisentan Macitentan Sildenafil Tadalafil Riociguat Epoprostenol IV Iloprost inhalation Treprostinil sc, inhalation	Epoprostenol IV
IIaC		Treprostinil IV	Bosentan Ambrisentan Macitentan Sildenafil Tadalafil Riociguat Iloprost inhalation Treprostinil sc, inhalation, IV
IIbC		Initial combination therapy	Initial combination therapy



Galie, et al. *J Am Coll Cardiol.* 2013;62(25):S60-72.

Interventional Procedures: Balloon Atrial Septostomy

- In order to:
  - Decompress right heart chambers
  - Increase left ventricle preload
  - Increase cardiac output
  - Improve systemic oxygen transport
  - Decrease sympathetic hyperactivity
- Creation of an interatrial right-to-left shunt
- Considered a palliative or bridging procedure
  - Patients refractory to medical therapy
  - Patients awaiting lung transplantation

Galie, et al. *J Am Coll Cardiol.* 2013;62(25):S60-72.

Interventional Procedures: Lung Transplantation

- Surgical procedures
  - Single lung transplant
  - Bilateral lung transplant – most common
  - Heart-lung transplant – increasingly less common, with about 70 – 90 performed every year*
- Lung transplantation remains the standard of care for patients with PAH who fail aggressive medical therapy, until the age of 75 (depending on the transplant center)

*Long, et al. *Pulm Circ*. 2011;1(3):327-33.
Galie, et al. *J Am Coll Cardiol.* 2013;62(25):S60-72.

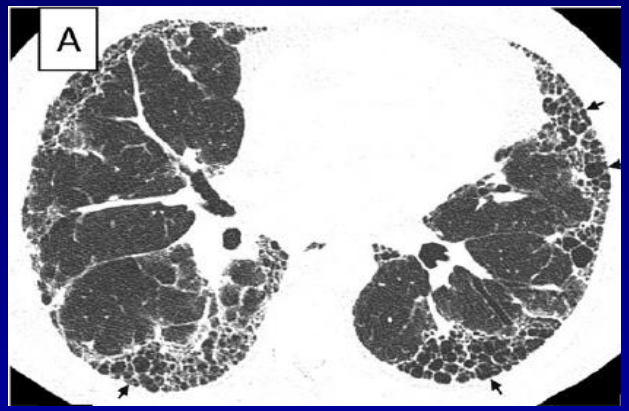
Role of Pulmonary Fibrosis

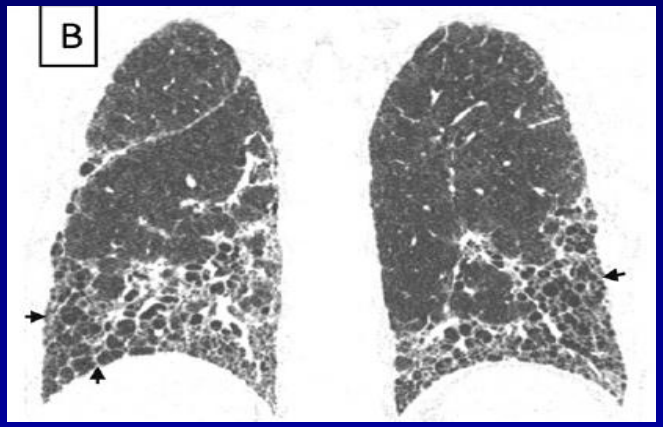
Idiopathic Pulmonary Fibrosis (IPF)

- Chronic, progressive, irreversible, and usually lethal
- Median age at diagnosis: 66
- Annual incidence: 4.6-16.3 per 100,000 people
- Slightly more common in men
- Risk factors: cigarette smoking and exposure to metal/wood dust
- Some families have a autosomal dominant vertical transmission pattern

King TE, et al. Lancet. 2011; 378: 1949-61.

Diagnosis





- Requires:
  - Exclusion of other known causes of interstitial lung disease
  - The presence of usual interstitial pneumonia (UIP) (A and B) pattern on high-resolution computed tomography (HRCT) in patients not subject to surgical lung biopsy
  - Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy

Raghu, 2011

Clinical Presentation

- Chronic and progressive exertional dyspnea and cough
- Inspiratory crackles
- Finger clubbing
- Median survival of 2.5-3.5 years after diagnosis
- Worse prognosis

Old age (>70 years)	Smoking history	Low BMI
Severe physiological impairment	Large radiological extent of disease	Pulmonary hypertension

King TE, et al. Lancet. 2011; 378: 1949-61.

Pathophysiology

- Pulmonary fibrosis is initiated by microvascular injury, which leads to endothelial cell damage and alveolar epithelial injury. This leads to activation of the coagulation cascade, release of various cytokines and growth factors, and ultimately activation of fibroblasts, a key event in the development of fibrosis.

New Therapies

- Nintedanib (Ofev): Approved Fall 2014
- Pirfenidone (Esbriet): Approved Fall 2014

Nintedinib (Ofev)

- Tyrosine kinase inhibitor: inhibits platelet-derived growth factor (PDGFR), fibroblast growth factor (FGFR), vascular endothelial growth factor (VEGFR), and Fms-like tyrosine kinase-3 (FLT3); binds competitively to the ATP binding pocket of these receptors and blocks intracellular signaling which is crucial for the proliferation, migration, and transformation of fibroblasts
- 150 mg every 12 hours (max: 300 mg daily)
- Not recommended in moderate to severe hepatic impairment (not studied); no renal adjustment
- Reduce dose to 100 mg every 12 hours for AST/ALT >3 but <5 x ULN (without signs of severe liver damage); do not use if AST/ALT >5x ULN or >3 with ssx of severe liver injury
- Administer with food (increases exposure by ~20%); do not crush/chew
- Highly protein bound (98%)

Nintedinib [package insert].

Nintedinib (Ofev. Cont.)

- No contraindications
- Warnings: may increase risk of bleeding; thromboembolic events including MI have been reported, caution in patients with high CV risk; diarrhea occurs in 62% of patients but was generally mild to moderate, treat with supportive care; increased risk of GI perforation; elevations of ALT/AST/GGT/alk phos/Tbili have been reported
- Pregnancy category D
- ADR: **diarrhea (62%),** nausea (24%), abdominal pain (15%), vomiting (12%), decreased appetite (11%), increased liver enzymes (14%)
- Monitoring: obtain LFTs prior to treatment, monthly for 3 months, and every 3 months thereafter

Nintedinib [package insert].

Pirfenidone (Esbriet)

- Precise MOA not fully understood; may decrease fibroblast proliferation and the production of fibroblast-associated proteins and cytokines; may decrease formation and accumulation of extracellular matrix; believed to exert anti-inflammatory properties
- Days 1 to 7: 267 mg 3 times daily; Days 8 to 14: 534 mg 3 times daily; Day 15 and thereafter: 801 mg 3 times daily; maximum dose in any patient: 2403 mg daily
- If therapy is interrupted for 14 or more days, **reinitiate the titration**
- Dose reduce for **strong 1A2 inhibitors** (fluvoxamine, ciprofloxacin)
- Not recommended in ESRD requiring dialysis or Child-Pugh class C liver impairment (not studied)
- For ALT/AST >3 to <5 without hyperbilirubinemia: may reduce dose (no recommendation for dosing provided); for ALT/AST>3 to <5 with hyperbilirubinemia: discontinue; for ALT/AST >5 ULN: discontinue.
- May consider dose adjustment for GI tolerance or photosensitivity
- Administer **with food** at the same time each day (decreases frequency of dizziness or nausea); do not open capsules

Pirfenidone [package insert].

Pirfenidone (Esbriet) (Cont.)

- No contraindications
- Warnings: angioedema; CNS effects, may cause dizziness/fatigue and patients should be cautioned about performing tasks that require alertness; GI effects, consider dose reduction, tolerance develops over first 3 months; increase ALT/AST and hyperbilirubinemia, monitor closely; photosensitivity, reported during the first 6 months of therapy, instruct patients to minimize exposure to the sun; weight loss, has been reported
- Pregnancy category C
- ADR: **fatigue (26%), HA (22%),** dizziness (18%), skin rash (30%), photosensitivity (12%, higher in Japanese patients), **nausea (36%), diarrhea (26%),** abdominal pain (24%), GERD (11%), URTI (27%)
- Monitoring: hepatic function at initiation, monthly x 6 months then every 3 months

Pirfenidone [package insert].

Summary

- Greater number of treatment options for PAH has advanced patient survival.
- Screening of high-risk patients is essential.
- Both a delay in diagnosis and misdiagnosis are common and have a catastrophic impact on outcomes.
- Right heart catheterization is mandatory for diagnostic confirmation.

Summary

- Management of patients with PAH involves a complex strategy which includes supportive therapy and disease-targeted medications.
- The evidence-based treatment algorithm for PAH streamlines decision making and drug selection.
- Combination therapy is the standard of care fo PAH when initial therapy becomes inadequate.
- The prognosis of Pulmonary Fibrosis remains poor despite the newly approved medications which are very expensive

Recently FDA Approved Medications

1. Corlanor (ivabradine)
2. Entresto (sacubitril and valsartan)
3. Stiolto Respimat (tiotropium bromide and olodaterol)
4. New Insulins and formulations: Tresiba (insulin degludec), Toujeo (insulin glargine 300 units/ml), Humalog U-200 (Lispro), Humulin R U-500 KwikPen, Ryzodeg (insulin degludec/aspart mix)
5. Praxbind (idarucizumab)
6. New Cholesterol Meds (Repatha and Praluent)

Corlanor (ivabradine)

- First in its class. A hyperpolarization-activated cyclic nucleotide-gatedchannel blocker

- Indications:

  Corlanor® (ivabradine) is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

- Reduces pacemaker activity of the sinoatrial node (SA node)
- Outcome: decrease in heart rate with no effect on ventricular repolarization or myocardial contractility

Corlanor (ivabradine) Adverse Effects

- Bradycardia (6-10%)
- Hypertension (9%) (although hypotension has been reported in postmarketing experience)
- Atrial fibrillation (5-8%)
- Visual symptom: luminous phenomena (3%)
  - described as increases in brightness in partial areas of the visual field (halos, image decomposition, colored bright lights, or multiple images)

Micromedex 2016

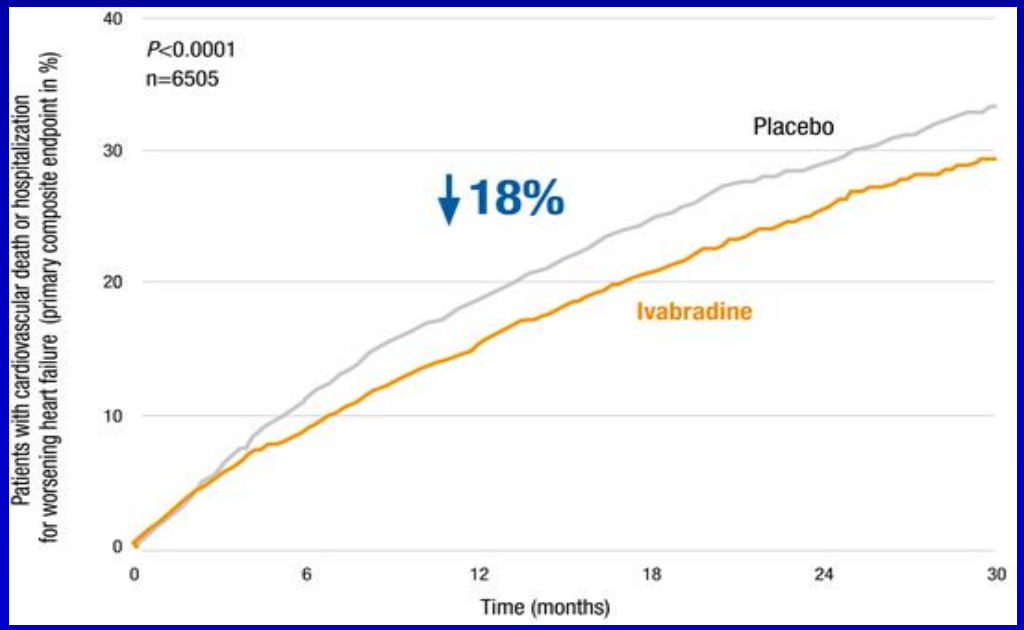
Corlanor (ivabradine) Contraindications

- Acute decompensated heart failure
- Blood pressure <90/50 mm Hg
- Sick sinus syndrome, sinoatrial block, or third-degree AV block (unless a functioning demand pacemaker is present)
- Resting heart rate <60 bpm prior to treatment
- Severe hepatic impairment or use with strong CYP3A4 inhibitors/inducers (metabolized by CYP3A4)
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker)

Micromedex 2016

Corlanor (ivabradine) SH/I_fT Trial

- Ivabradine significantly reduces risks associated with heart failure:
  - 18% reduction in CV death or hospital readmission for worsening HF
    - number needed to treat (NNT)= 26 patients at 1 year



Entresto (sacubitril and valsartan)

- Company: Novartis
- Approval date: July 2015 (fast tracked)

- Indications:
  - label: chronic heart failure

- Preparation & Pricing
  - Tablets (Entresto Oral)
    - 24-26 mg
    - 49-51 mg
    - 97-103 mg

Entresto Package Insert

Entresto Mechanism of Action

- Combination Drug
- First-in-class Neprilysin inhibitor
- Prodrug Sacubritil is converted to LBQ657 which is the inhibitor
- Valsartan blocks the angiotensin II type-1 (AT1) receptor, inhibiting angiotensin II and the release of aldosterone

Entresto Package Insert

Entresto Adverse Effects

11.5% discontinued therapy due to renal impairment with enalapril versus only 6% with Entresto

Adverse Effect	Entresto	Enalapril
Angioedema	0.5%	0.2%
Hypotension	18%	12%
Impaired renal function	6%	5%
Hyperkalemia	12%	14%
Cough	9%	13%

Entresto Contraindications

- History of angioedema related to previous ACE inhibitor or ARB treatment
- Concomitant use or use within 36 hours of ACE inhibitors
- Concomitant use of the direct renin inhibitor, Tekturna (aliskiren), in patients with diabetes

Stiolto Respimat (tiotropium bromide and olodaterol)

- Company: Boehringer Ingelheim
- Approval date: May 2015
- Indications:
  - label: COPD maintenance, including chronic bronchitis and emphysema
- Preparation Inhaler with a cartridge (2.5-2.5 mcg/ACT)
    - (60 inhalations/cartridge)

Stiolto Respimat Mechanism of Action

- Tiotroprium bromide – anticholinergic
  - inhibits M_3-receptors in smooth muscle leading to bronchodilation
- Olodaterol – long-acting beta2-adrenergic agonist (LABA)
  - activates B2 adrenergic receptors in the airways leading to elevation of cAMP levels
    - cAMP elevation leads to bronchodilation

Stiolto Respimat Adverse effects

- Nasopharyngitis (12.4%)
- Cough (3.9%)
- Back pain (3.6%)

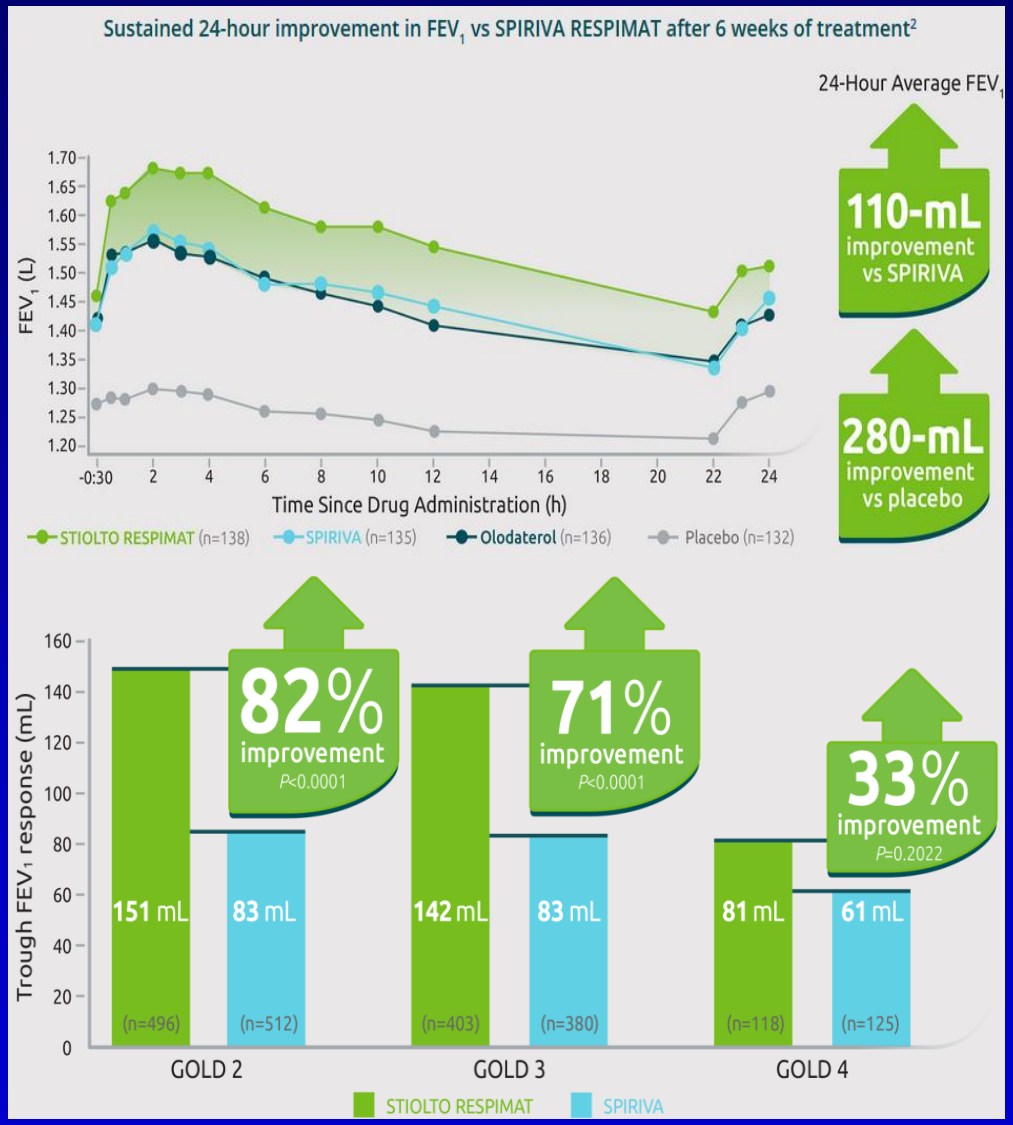
- Adverse events leading to discontinuation:
  - ✖ 8.7% in tiotroprium 2.5 mcg
  - – 9% in tiotroprium 5 mcg
  - – 5.5 % in tiotroprium + olodaterol 2.5/5 mcg
  - – 7.4% in tiotroprium + olodaterol 5/5 mcg

Stiolto Respimat Contraindications

- Hypersensitivity reactions
- All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication
- Stiolto shouldn’t be initiated in patients with acutely deteriorating COPD
- Stiolto shouldn’t be used as rescue therapy for acute symptoms

Stiolto Respimat GOLD 2-4 trials

- Stiolto Respimat demonstrated a 2.3 times greater FEV1 within 5 minutes after the first dose
- Sustained the FEV1 improvement benefit for around 22 hours after administration
- Showed an improvement in FEV1 across the range of GOLD staged COPD patients



Insulin Glargine U-300

- Approved in the US as Toujeo® in February 2015
- Nearly identical rates of HgA1c control compared to Glargine U-100
- 300 units/ml vs. 100 units/ml
  - Results in a smaller volume to be administered
  - Ideal for patients with high basal insulin needs
- Patients should dial the same number of units on both pens
  - For example: 40 units on Glargine U-100 pen = 40 units on Glargine U-300 pen

glargine U-300) product information

Insulin Degludec

- Available formulations : Insulin degludec (Tresiba®) 100 units/ml (U-100) and 200 units/ml (U-200)
- FDA approved in September 2015
- Daily subcutaneous injection for Type I and Type II diabetes
- Mechanism: longer acting basal insulin
- Lasts up to 42 hours after injection
- Lowers HgA1c roughly the same as glargine but may be associated with fewer episodes of nighttime hypoglycemia
- Insulin degludec pen's dose window shows the number of insulin units to be delivered. No dose conversion needed
- Exists in soultion as di-hexamers, convereted to multi-hexamers following SubQ injection then forms monomers which lead to slow absorption

Tresiba® (insulin degludec injection) product information

Insulin Lispro U-200 Kwikpen

- Approved in May 2015 in a pen only
- Holds twice as many units of insulin (600 units vs. 300 units) as the original U-100 pen in the same three-milliliter cartridge
- Conversion 1:1 (Not recommended if < 7 units of mealtime insulin per meal)
- Half the volume
- Once opened, Humalog® prefilled pens should be thrown away after 28 days, even if insulin remains.

Humalog (package insert). Eli Lilly and Company; 2015

Insulin U-500 Pen (Humulin R®)

- Available April 2016
- No dose conversion needed
- Dials in 5-unit increments
- Delivers up to 300 units in a single injection
- Holds 1500 units of insulin in every pen
- Same size as the other KwikPens
- Consider in patients requiring > 200 units/day and those with volume challenges such as multiple injections/dose or lipohypertrophy

Humulin R® U-500 Insulin Pen product information. Eli Lilly and Co. 2016. Indianapolis Indiana

Ryzodeg® (70% insulin degludec, 30% insulin aspart)

- Contains 70% long acting and 30% rapid acting insulin
- Cannot adjust basal insulin without adjusting bolus insulin and vice versa
- Administer once or twice daily with any meal
- May use another mealtime insulin with other meals if needed
- Recommended time between dose increases is 3-4 days

Ryzodeg (70% insulin degludec, 30% insulin aspart) Product information

Praxbind (idarucizumab)

Praxbind (idarucizumab)

- FDA approved: October 2015
- Brand: Boehringer Inhgelheim Pharmaceuticals
- **Indication: Injectable for Reversal of dabigatran (Pradaxa):**
  - Reversal of the anticoagulation effects of dabigatran for emergency surgery/urgent procedures OR in life-threatening or uncontrolled bleeding

Praxbind [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2015.

Adverse Reactions

- Headache
- Delirium
- Hypokalemia
- Constipation
- Fever
- Pneumonia
- Hypersensitivity

Idarucizumab. Lexi-Comp Online™, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; Accessed: March 30, 2016

Statin Therapy

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

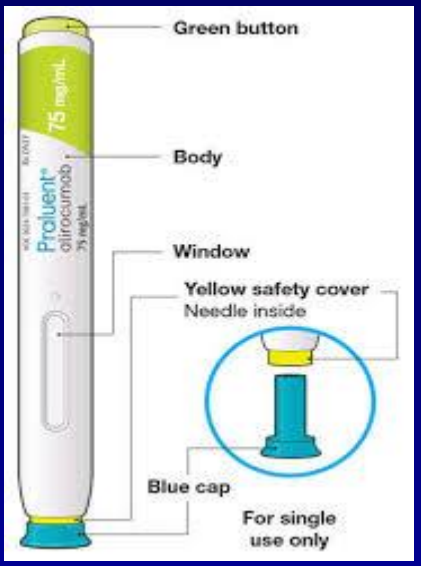
High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20 *(40)* mg**	**Atorvastatin 10 *(20)* mg** **Rosuvastatin (*5*) 10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40 *(80)* mg** **Lovastatin 40 mg** ***Fluvastatin XL 80 mg*** **Fluvastatin 40 mg bid** ***Pitavastatin 2–4 mg***	***Simvastatin 10 mg*** **Pravastatin 10–20 mg** **Lovastatin 20 mg** ***Fluvastatin 20–40 mg*** ***Pitavastatin 1 mg***

Stone, Neil et al. "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines." *Circulation*, 85. Web 13 Nov. 2013.

PCSK9 Inhibitors

- For Statin Non-Responders
- proprotein convertase subtilisin kexin type 9 (PCSK9)
- Binds LDL particles, undergoes endocytosis and clears LDL from the body

Alirocumab (Praluent®)



- Indication
  - heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic cardiovascular disease (ASCVD)
- Dosing
  - 75 mg SubQ every 2 weeks
  - 150 mg SubQ every 2 weeks if adequate response not achieved in 4-8 weeks
- Cost
  - ~$14,600/year

Praluent Package Insert

Evolucumab (Repatha™)

- Indication and dosing
  - Adjunct to diet and statin therapy for HeFH or ASCVD
    - 140 mg SubQ every 2 weeks
    - 420 mg SubQ once monthly
  - Adjust to diet and other LDL-lowering therapies for homozygous familial hypercholesterolemia (HoFH)
    - 420 mg SubQ once monthly
- Cost
  - ~$14,100/year

Repatha Package Insert

Safety

- Common adverse effects: injection site reactions, nasopharyngitis, influenza and upper respiratory infections
- No reported myalgias, liver enzyme increases or increased risk of diabetes
- Neurocognitive adverse effects?

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