

New Drug Update 2015-16 October 2016

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Faculty Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.
- I do not speak for or consult with any pharmaceutical manufacturer.

CAPiTA Trial Preliminary Results

- **The 85,000-patient study in the Netherlands**, called CAPiTA, showed that Prevnar 13 prevented invasive pneumococcal disease, meaning infections of Streptococcus pneumoniae bacteria in patients age 65 and older.
 - **45.56% fewer first episodes of vaccine-type CAP among Prevnar 13-vaccinated subjects than in subjects who received placebo** (P=0.0006).
 - Secondary objectives, the Prevnar 13 group experienced 45.00 % fewer first episodes of non-bacteremic/non-invasive vaccine-type CAP (P=0.0067) and 75.00 % fewer first episodes of vaccine-type IPD (P=0.0005) compared with the placebo group
 - **To be reviewed by ACIP and FDA**

ACIP Meeting Feb 26, 2015

- Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) **voted to include GARDASIL[®]9 (Human Papillomavirus 9-valent Vaccine, Recombinant) in the recommendations for use of HPV vaccines. GARDASIL 9 has been added to the routine recommendations for vaccination of 11- and 12-year-old females and males.**
 - The vaccination series can be started at age nine. Vaccination is also recommended for females aged 13 to 26 and for males aged 13 to 21 who have not been vaccinated previously or have not completed the 3-dose series.
 - GARDASIL 9 has been added to the CDC's Vaccines for Children (VFC) program for both boys and girls.

ACIP Meeting June 2016

- GlaxoSmithKline has decided to withdraw its 2vHPV vaccine from the U.S. market by November 2016, and Merck will withdraw its HPV-4 vaccine by the end of 2016, leaving only the HPV-9 vaccine available in the United States.
- ACIP discussed the data on a two dose series of HPV-9 in 9-14 girls which was as effective as the 3 dose series in girls 15-26 y/o as long as the second dose is administered 6-12 mo after the first dose. If the second dose is given prior to 6 mo a 3 doses series is indicated. The ACIP did not vote and no recommendations are being issued at this time for the 2 dose series.

Valsartan/Sacubitril - Entresto

- FDA approved 7-8-2015 indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.
- It is usually administered in conjunction with other heart failure therapies including an evidence based beta blocker and when appropriate an aldosterone antagonist, and replaces the ACE inhibitor or other ARB.
 - Film-coated tablets (sacubitril/valsartan): 24/26 mg; 49/51 mg; 97/103 mg for BID dosing
 - Cost: \$12.50 per day or \$375.00/mo (WAC)

Valsartan/Sacubitril - Entresto

- If switching from an ACE inhibitor to (sacubitril/valsartan) allow a washout period of 36 hours between administration of the two drugs
- The recommended starting dose is 49/51 mg (sacubitril/valsartan) twice-daily.
- Double the dose of after 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) twice-daily, as tolerated by the patient.
- Reduce the starting dose to 24/26 mg (sacubitril/valsartan) twice-daily for:
 - patients not currently taking an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) or previously taking a low dose of these agents
 - patients with severe renal impairment
 - patients with moderate hepatic impairment

Valsartan/Sacubitril - Entresto

- **Box Warning: Fetal toxicity - d/c with pregnancy**
- **Contraindications:**
 - History of angioedema related to previous ACE inhibitor or ARB therapy.
 - Concomitant use with ACE inhibitors.
 - Concomitant use with aliskiren in patients with diabetes.
- **Warnings/Precautions:**
 - Observe for signs and symptoms of angioedema and hypotension.
 - Monitor renal function and potassium in susceptible patients.

Valsartan/Sacubitril - Entresto

- In the **double-blind period of PARADIGM-HF, 0.5% of patients treated with (valsartan/sacubitril) and 0.2% of patients treated with enalapril had angioedema.**
 - associated with a higher rate of angioedema in Black than in non-Black patients

PARADIGM-HF Trial

- Compared the angiotensin-neprilysin inhibitor LCZ696 (200 mg BID) with the angiotensin converting enzyme inhibitor enalapril (10 mg BID) in 8399 patients with heart failure and reduced ejection fraction (<35%, NYHA Class II-IV) able to tolerate ACEI or ARB and also on stable doses of beta blocker/mineralocorticoid antagonist unless not tolerated, in a double-blind trial. (NOTE only 5% of pts were black and <10% from North America)
- 200 mg of LCZ696 delivers the equivalent of 160 mg of valsartan (evidence-based dose of valsartan in HF and post MI)

• DOI: 10.1161/CIRCULATIONAHA.114.013748

PARADIGM-HF Trial

- After a mean of 27 months follow up the LCZ696-treated patients as compared to the enalapril treated patients required:
 - Less intensification of medical treatment for heart failure (520 versus 604; hazard ratio, 0.84; 95% confidence interval, 0.74–0.94; P=0.003)
 - Fewer emergency department visit for worsening heart failure (hazard ratio, 0.66; 95% confidence interval, 0.52–0.85; P=0.001).
 - Fewer hospitalizations for worsening heart failure (851 versus 1079; 23% reduction P<0.001)
 - Less hospitalization for any cause; annualized rates of 30.3% and 26.3% respectively. These differences reflected a 12.6% RRR; ARR 4.0%; NNT 25 with LCZ696 instead of enalapril (hazard ratio, 0.87; 95% CI, 0.82–0.93; P<0.0001).
 - Less likely to require intensive care (768 versus 879; 18% reduction, P=0.005).
 - All cause mortality: 835 patients in the enalapril group and 711 in the LCZ696 group, corresponding to annualized rates of 7.5% and 6.0%, respectively. HR 0.84 (95% CI 0.76-0.93 p=0.0009); RRR 16%; ARR 1.5%; NNT 67

• DOI: 10.1161/CIRCULATIONAHA.114.013748

Valsartan/Sacubitril – Entresto in PARADIGM - HF

- Mean daily doses achieved were LCZ696 375 mg and enalapril 18.9 mg; 76% and 75% of LCZ696 and enalapril patients, respectively, maintained the target dose through the end of the study.
- Incidence of symptomatic hypotension was 14% with LCZ696 and 9.2% with enalapril (P < 0.001); number needed to harm (NNH) with LCZ696 was 20.8.
- Incidence of serum creatinine elevated to at least 2.5 mg/dL was 3.3% with LCZ696 and 4.5% with enalapril (P = 0.007); NNH with enalapril was 83.3.
- Incidence of serum potassium greater than 6 mmol/L was 4.3% with LCZ696 and 5.6% with enalapril (P = 0.007); NNH with enalapril was 76.9.
- Incidence of cough was 11.3% with LCZ696 and 14.3% with enalapril (P < 0.001); NNH with enalapril was 33.3.

Valsartan/Sacubitril – Entresto in PARADIGM - HF

- **Estimating the Long-Term Treatment Benefits of Sacubitril–Valsartan** (N Engl J Med 2015; 373:2289-2290)
- Using actuarial estimates from the PARADIGM-HF trial, and assuming that the protective effects of sacubitril–valsartan remain consistent with long-term use, we extrapolated from the available short-term follow-up data to **estimate that treatment with sacubitril–valsartan would result in a projected benefit of 1 to 2 years of increased life expectancy and survival free from heart failure for patients (45 to 75 years of age) such as those in the PARADIGM-HF trial.**

Valsartan/Sacubitril – Entresto

- **A recent analysis on JAMA Cardiology reports that 84% of heart failure patients with reduced ejection fraction--the population Entresto is approved to treat-- would be eligible for therapy with Entresto. That's almost 2.3 million patients. Using the drug properly in these patients could prevent 28,484 deaths every year, the study concluded, or a range of 18,230 to 41,017 per year.**

• JAMA Cardiol. doi:10.1001/jamacardio.2016.1724 Published online June 22, 2016.

Valsartan/Sacubitril – Entresto and Alzheimers?

- **Nepilysin degrades multiple peptides including angiotensin, endothelin 1, adrenomedullin, opioids, bradykinin, and amyloid- β peptide (A β).**
 - In animal models, neprilysin plays a critical role in maintaining the homeostasis of A β in the brain and an **accumulation of A β in the brain is associated with the pathogenesis of Alzheimer disease.**
 - Disruption of the neprilysin gene elevated oligomeric A β levels in the brain and accelerated the development of cognitive dysfunction in a genetic mouse model of Alzheimer disease
 - Studies in the eye suggest that a similar pathogenic mechanism **may contribute to the development of age-related macular degeneration?**
 - JAMA (January 5), 2016; 315: 25-26

New Focused Update on New Pharmacologic Therapy for Heart Failure

- **Recommendation for ARNI (angiotensin receptor – neprilysin inhibitor) i.e.. valsartan/sacubitril - Entresto**
 - **“The clinical strategy of inhibition of the renin angiotensin system with ACE inhibitors (COR 1/LOE A) or ARB (COR 1/LOE A) or ARNI (COR 1/LO#E B-Randomized) in conjunction with evidence-based beta blockers and aldosterone antagonists in selected patients is recommended for patients with chronic HFrEF to reduce morbidity and mortality”**
 - Journal of the American College of Cardiology (2016), doi: 10.1016/j.jacc.2016.05.011.

New Focused Update on New Pharmacologic Therapy for Heart Failure

- **“In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.’ (COR 1/LOE B-R)**
- **“ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.” (COR III Harm/LOE B-R)**
- **“ARNI should not be administered to patients with a history of angioedema” (COR III harm/LOE EO)**
 - Journal of the American College of Cardiology (2016), doi: 10.1016/j.jacc.2016.05.011.

Ivabradine – Corlanor by Amgen

- **April 15, 2015 The FDA approved ivabradine (Corlanor, Amgen) for reducing the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction of 35% or less, who are in sinus rhythm with resting heart rate of 70 bpm or more, and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use. The drug acts by blocking the hyperpolarization-activated cyclic nucleotide-gated channel responsible for the cardiac pacemaker.**

Ivabradine – Corlanor

- **Ivabradine causes a dose-dependent reduction in heart rate. The size of the effect is dependent on the baseline heart rate (i.e., greater heart rate reduction occurs in subjects with higher baseline heart rate). At recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise.** Analysis of heart rate reduction vs. dose indicates a plateau effect at doses > 20 mg twice daily.
- **Ivabradine slows the rate of the heart by inhibiting the so-called "funny" current within the heart's natural pacemaker, the sinoatrial node.**
- **Ivabradine does not have negative inotropic effects.**

Ivabradine – Corlanor

SHIFT Trial

- **The Systolic Heart failure treatment with the *I*/inhibitor ivabradine Trial (SHIFT) was a randomized, double-blind trial comparing Ivabradine and placebo in 6558 adult patients with stable NYHA class II to IV (primarily II and III) heart failure, left ventricular ejection fraction ≤ 35%, and resting heart rate ≥ 70 bpm. Patients had to have been clinically stable for at least 4 weeks on an optimized and stable clinical regimen, which included maximally tolerated doses of beta-blockers and, in most cases, ACE inhibitors or ARBs, spironolactone, and diuretics, with fluid retention and symptoms of congestion minimized. Patients had to have been hospitalized for heart failure within 12 months prior to study entry.**

Ivabradine – Corlanor

Endpoint	Ivabradine		Placebo		HR 95% CI	P-value	ARR/NNT
	N=3241 N	%	N=3264 N	%			
Primary composite of time to first hospitalization for HF and CV death	793	24.5%	937	28.7%	0.82 (0.75-0.90)	<0.0001	4.2%/24
Hospitalization for worsening HF	505	15.6%	660	20.2%	0.74 (0.66-0.83)	<0.0001	4.6%/24
CV death as first event	288	8.9%	277	8.5%			

Mean follow-up 23 months. Ivabradine's benefit on the primary endpoint in SHIFT appeared to decrease as the dose of beta-blockers increased, with little if any benefit demonstrated in patients taking guideline-defined target doses of beta-blockers.

Ivabradine – Corlanor

Adverse Effects from SHIFT Trial:

Bradycardia	10%	2.2%
Hypertension	8.9%	7.8%
Atrial Fibrillation	8.3%	6.6%
Phosphenes, visual brightness*	2.8%	0.5%

*Phosphenes are phenomena described as a transiently enhanced brightness in a limited area of the visual field, halos, image decomposition (stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistency).

Postmarketing reports: syncope, hypotension, angioedema, erythema, rash, pruritus, urticaria, vertigo, diplopia, and visual impairment.

Ivabradine – Corlanor

Dosage Adjustment Table

Heart Rate	Dose Adjustment
> 60 BPM	Increase dose by 2.5 mg BID up to a maximum dose of 7.5 mg BID
50-60 BPM	Maintain the dose
< 50 BPM	Decrease the dose by 2.5 mg BID, if current dose is 2.5 mg BID discontinue therapy

Available as a scored 5 mg tablet and 7.5 mg unscored tablet
 Cost is reported to be ~\$375.00 per month wholesale

New Focused Update on New Pharmacologic Therapy for Heart Failure

- **Recommendation for Ivabradine - Corlanor**
 - “Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving Guideline Directed Evaluation and Management (GDEM), including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.” COR IIa/LOE B-R)
 - Journal of the American College of Cardiology (2016), doi: 10.1016/j.jacc.2016.05.011.

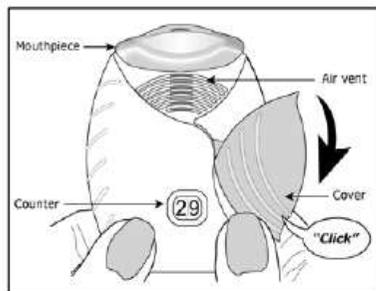
Umeclidinium and Vilanterol – Anoro Ellipta Inhaler by GSK

- A combination of umeclidinium, an anticholinergic (LAMA), and vilanterol, a long-acting beta2-adrenergic agonist (LABA), indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).
- Not indicated for the relief of acute bronchospasm or for the treatment of asthma

Umeclidinium and Vilanterol – Anoro Ellipta Inhaler



Umeclidinium and Vilanterol – Anoro Ellipta Inhaler



Be careful, every time you move the cover you move to the next dose!

Umeclidinium and Vilanterol – Anoro Ellipta Inhaler

- Both components may increase CV risk?
 - A dose-dependent increase in heart rate was observed (~9-20 Beats per minute increase with higher than recommended doses)
- Adverse Effects:
 - include pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain, and chest pain.
- Cost: ~\$330.00/ 30 doses Goodrx.com

Umeclidinium – Incruse Ellipta Inhaler

- INCRUSE™ ELLIPTA® 62.5 mcg/ dose is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
- The effective half-life after once daily dosing is 11 hours.
- Trough FEV1 (mL) at Day 169: Difference From Placebo (95% CI) n = 280 115ml (76, 155)
- Cost ~ \$250.00 Goodrx.com

Umeclidinium – Incruse Ellipta Inhaler



Olodaterol - Striverdi Respimat by Boehringer Ingelheim

- FDA approved July 31, 2014 - **Olodaterol is a long-acting once a day beta-adrenergic agonist (LABA) for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD),** including chronic bronchitis and/or emphysema with airflow obstruction.
 - Each actuation from the mouthpiece contains 2.7 mcg olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol. Two actuations equal one dose of 5 mcg at the same time each day.

Tiotropium – Spiriva Respimat 2.5 mcg/inhalation for COPD



Tiotropium – Spiriva Respimat 1.25 mcg/inhalation for Asthma

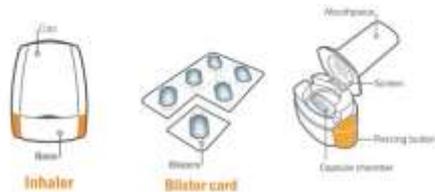
- **Blue cap color is for patients with asthma!**



Glycopyrrolate – Seebri Neohaler by Novartis

- Oct 29, 2015 The U.S. Food and Drug Administration (FDA) approved Seebri Neohaler (glycopyrrolate) inhalation powder, a long-acting muscarinic antagonist (LAMA) indicated for the long-term maintenance treatment of airflow obstruction in patients 18 and older with chronic obstructive pulmonary disease (COPD).
- Dosed twice a day by inhalation (15.6 mcg /capsule for inhalation)
- Cost: \$330.00/60 capsules GoodRx.com

Glycopyrrolate – Seebri Neohaler



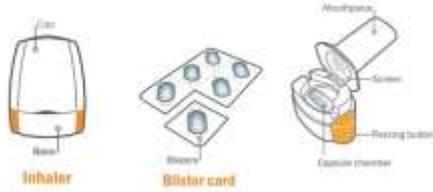
Store SEEBRI capsules in the blister, and only remove IMMEDIATELY BEFORE USE with the NEOHALER device. Each capsule contains approximately 25 mg of lactose monohydrate (which contains trace levels of milk protein).



Combination of Glycopyrrolate and Indacaterol – Utibron Neohaler by Novartis

- Oct 29, 2015 the FDA approved the combo of glycopyrrolate and indacaterol (a BID LABA/LAMA) for the maintenance treatment of patients with COPD.
 - Capsules contain 27.5 mcg of indacaterol and 15.6 mcg glycopyrrolate inhalation powder for use with the NEOHALER device
 - Administered at the same time of the day, (1 capsule in the morning and 1 capsule in the evening), every day.
 - Cost: \$330.00/60 capsules GoodRx.com

Glycopyrrolate and Indacaterol – Utibron Neohaler



Store Utibron capsules in the blister, and only remove IMMEDIATELY BEFORE USE with the NEOHALER device. Each capsule contains approximately 25 mg of lactose monohydrate (which contains trace levels of milk protein).



Combination of Tiotropium and Olodaterol - Stiolto Respimat

- 5/21/2015 the FDA approved Boehringer Ingelheims **Fixed-Dose Combination Tiotropium Plus Olodaterol – Stiolto for Patients with COPD. (LAMA + LABA)**
 - The NDA submission for tiotropium + olodaterol FDC is based on results from three global Phase III trials – the 52-week replicate TONADO® 1&2 studies and the 6-week cross-over VIVACITO® dose finding study.
 - The phase III clinical trial program (TOViTO®) for tiotropium + olodaterol includes more than 7,000 people living with varying severities of COPD worldwide.
 - Stiolto Respimat Inhalation Spray: 60 metered actuations (NDC 0597-0155-61)
 - Cost: ~ \$325.00

Tiotropium and Olodaterol - Stiolto Respimat



Global Strategy for Diagnosis, Management and Prevention of COPD
Manage Stable COPD: Pharmacologic Therapy
(Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)

Patient	Recommended First choice	Alternative choice	Other Possible Treatments
A	SAMA pm or SABA pm	LAMA or LABA or SABA and SAMA	Theophylline
B	LAMA or LABA	LAMA and LABA	SABA and/or SAMA Theophylline
C	ICS + LABA or LAMA	LAMA and LABA or LAMA and PDE4-inh. or LABA and PDE4-inh.	SABA and/or SAMA Theophylline
D	ICS + LABA and/or LAMA	ICS + LABA and LAMA or ICS+LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.	Carbocysteine SABA and/or SAMA Theophylline

Arnuity Ellipta (fluticasone furoate inhalation powder) by GSK/Theravance

- **FDA approved August 20, 2014 ARNUITY ELLIPTA is a corticosteroid indicated for: once-daily maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. Not indicated for relief of acute bronchospasm.**

– Following repeat-dose inhaled administration, the plasma elimination phase half-life averaged 24 hours.

Arnuity Ellipta (fluticasone furoate inhalation powder)

- **In a 343 patient placebo controlled trial 100 mcg fluticasone furoate QD was similar to 250 mcg of fluticasone propionate BID**
- Available in 100 and 200 mcg/inhalation Ellipta 30 dose dry powder inhaler
- **Cost ~ \$150.00 per 100 mcg and ~\$200.00/200 mcg Goodrx.com**
- Also available in 14 blisters (institutional pack).

Arnuity Ellipta (fluticasone furoate inhalation powder)



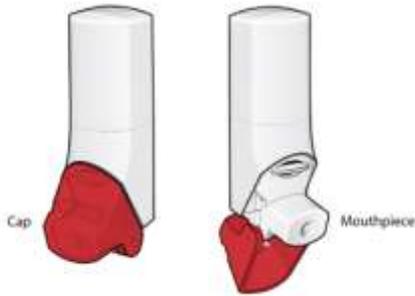
Albuterol sulfate inhalation powder – ProAir Respiclick by Teva

- FDA approved 4-1-2015 for treatment (1-2 inhalations up to every 4-6 hours) or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm (15-30 min before exercise) in patients 12 years of age and older.
- April 29, 2016 now FDA approved for children 4-11 years of age.
- DO NOT USE with a spacer!

PROAIR RESPICLICK (albuterol sulfate) inhalation powder

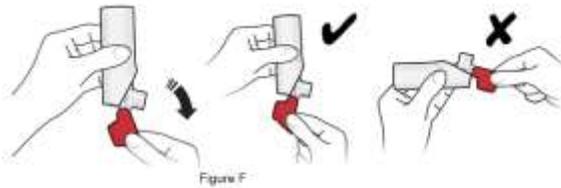
- PROAIR RESPICLICK is a multi-dose breath-actuated dry powder inhaler that meters 117 mcg of albuterol sulfate (equivalent to 97 mcg of albuterol base) from the device reservoir and delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouth piece per actuation.
 - 200 actuations per device with a dose counter
 - No priming required! Cost: ~ \$55.00
 - Do Not wash or put any part of your inhaler in water

PROAIR RESPICLICK (albuterol sulfate) inhalation powder



PROAIR RESPICLICK (albuterol sulfate) inhalation powder

Step 2. Hold the inhaler upright as you open the cap fully. See Figure F.



- Open the cap all the way back until you hear a "click".
- Your PROAIR RESPICLICK inhaler is now ready to use.
- Do not open the cap unless you are taking a dose.

FDA Pulls Approval of Niacin, Fibrate in Combo with Statins

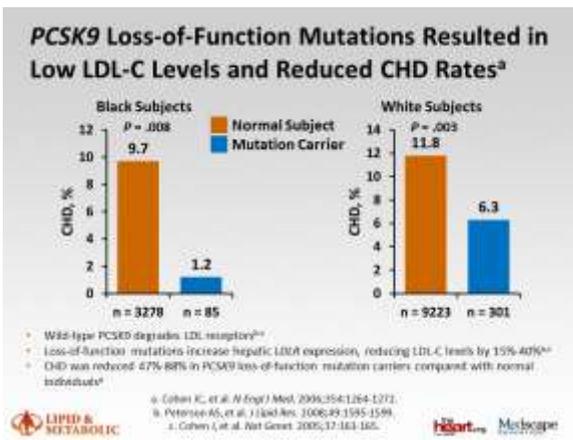
- **4-15-2016 Citing a lack of cardiovascular benefit, the FDA is taking the unusual step of withdrawing approvals it had previously given for use of niacin and fenofibric acid with statins to treat high cholesterol.**
- The decision affects the indication of niacin extended-release (Niaspan, AbbVie) and fenofibric acid (Trilipix, AbbVie), as well as AbbVie's Advicor and Simcor, both of which combine niacin with a statin.

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of ASCVD Risk (JACC July 2016, 68:92-125)

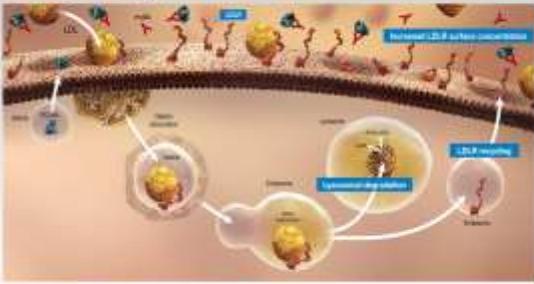
- Ezetimibe is the first nonstatin medication that should be considered in most of the patient scenarios, given its safety and tolerability, as well as demonstrated, though modest, efficacy when added to moderate-dose statin in one trial of patients with acute coronary syndrome.
- Bile acid sequestrants (BAS) may be considered as second-line therapy for patients in whom ezetimibe is not tolerated, but they should be avoided in patients with triglycerides greater than 300 mg/dL.
- Alirocumab and evolocumab may be considered if the goals of therapy have not been achieved on maximally tolerated statin and ezetimibe in higher-risk patients with clinical ASCVD or FH. Given the lack of long-term safety and efficacy data on these agents, they are not recommended for use in primary prevention patients in the absence of FH.

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of ASCVD Risk (JACC July 2016, 68:92-125)

- For patients with homozygous hypercholesterolemia, referral to a lipid specialist is strongly recommended with statins, and nonstatins including ezetimibe, BAS, with consideration for use of lomitapide, mipomersen, and LDL apheresis as necessary. LDL apheresis is also approved for heterozygous FH.
- In selected high-risk patients, such as those with existing ASCVD or LDL cholesterol level of 190 mg/dL or greater, use of nonstatins may be considered if maximally tolerated statin therapy has not achieved greater than 50% reduction in LDL cholesterol from baseline.



Impact of PCSK9 Monoclonal Antibodies on LDL Receptor Surface Concentrations



Alirocumab-Praluent by Sanofi/Regeneron

- **July 24, 2015** the FDA approved alirocumab as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.
- The effect of alirocumab on cardiovascular morbidity and mortality has not been determined.

Alirocumab-Praluent

- Supplied in single-dose pre-filled pens and single-dose pre-filled glass syringes. Each pre-filled pen or pre-filled syringe is designed to deliver 1 mL of 75 mg/mL or 150 mg/mL solution. (available in cartons containing 1 or 2, pre-filled pens and 1 or 2, pre-filled syringes).
- **Cost: \$14,600.00/year**



ODYSSEY Long Term Trial

- The, reported by Dr. Jennifer Robinson, University of Iowa, included **2,341 patients with hypercholesterolemia at very high risk, including patients with heterozygous FH (18%), who were on maximally tolerated statin therapy (44% on high-dose intensive statin therapy) with or without other lipid lowering treatment. Baseline LDL cholesterol was 122 mg/dL. All patients were randomized to double-blind treatment with alirocumab (150 mg every 2 weeks, n=1553) or placebo (n=788) every 2 weeks for up to 78 weeks.** ESC Congress August 31, 2014

ODYSSEY Long Term Trial

- **At week 24, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL cholesterol level was -62 percentage points (P<0.001); the treatment effect remained consistent over a period of 78 weeks.**
– N Engl J Med 2015; 372:1489-1499

ODYSSEY Long Term Trial

- The alirocumab group, as compared with the placebo group, at 78 weeks had higher rates of **injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%).**
– N Engl J Med 2015; 372:1489-1499

ODYSSEY Long Term Trial

- In a post hoc analysis, **the rate of major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) at 78 weeks was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal P=0.02).**

– N Engl J Med 2015; 372:1489-1499

Evolocumab – Repatha by Amgen

- FDA approved 8-27-2015 a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated as an adjunct to diet and: for the treatment of patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol(LDL-C).
- Patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C when other LDL-C lowering therapies are not adequate (e.g., statins, ezetimibe, LDL apheresis).

Evolocumab – Repatha

- The effect of evolocumab on cardiovascular morbidity and mortality has not been determined.
- Available as:
 - Injection: 140 mg/mL in a single –use prefilled syringe
 - Injection: 140 mg /mL in a single –use prefilled SureClick[®] autoinjector
 - Cost: \$542.31/140 mg dose WAC or about \$14,100.00/year for the every other week dosage.
 - (The company is planning on marketing a 420 mg syringe early next year but until then they say they will work with insurers to assure better pricing on the 3 x 140 mg once monthly dosing)
 - Storage:
 - Keep in the refrigerator. Prior to use, allow to warm to room temperature for at least 30 minutes. Alternatively, for patients and caregivers, the drug can be kept at room temperature (up to 25°C (77°F)) in the original carton. However, under these conditions, the medication must be used within 30 days.

Evolocumab – Repatha

- **7/11/2016 The FDA approved Pushtronex system is an on-body infusor with a prefilled cartridge of evolocumab 420 mg for once a month administration.**
 - Amgen said that **the device adheres to the body and is hands-free.** While receiving the injection, patients are able to perform moderate physical activities. The system was developed in collaboration with West Pharmaceutical Services.
- Price is expected to be similar to the 140 mg every 2 weeks or about \$14,100.00/year

Evolocumab – Repatha



Repatha® (evolocumab) Pushtronex™ system (on-body infusor with prefilled cartridge)

- The Pushtronex system will be available to patients in the U.S. in early August.

Evolocumab – Repatha

- Administer by **subcutaneous injection**
- Primary hyperlipidemia with established **clinical atherosclerotic CVD or HeFH:**
 - **140 mg every 2 weeks or 420 mg* once monthly in abdomen, thigh, or upper arm**
- **HoFH:**
 - **420 mg* once monthly**
 - ***To administer 420 mg, give 3 x 140 mg injections consecutively within 30 minutes**

Evolocumab – Repatha

- Data in patients with heterozygous familial hypercholesterolemia (HeFH):
- A multicenter, double-blind, randomized, placebo-controlled, **12-week trial in 329 patients with heterozygous familial hypercholesterolemia (HeFH) on statins with or without other lipid-lowering therapies. Patients were randomized to receive subcutaneous injections of evolocumab 140 mg every two weeks, 420 mg once monthly, or placebo.**
 - The average LDL-C at baseline was 156 mg/dL with 76% of the patients on high-intensity statin therapy

Evolocumab – Repatha

- Results after 12 weeks:
 - In these patients with HeFH on statins with or without other lipid lowering therapies, the **differences between evolocumab and placebo in mean percent change in LDL-C from baseline to Week 12 was -61% (95%CI: -67%, -55%; p < 0.0001) and -60% (95%CI: -68%, -52%; p < 0.0001) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively.**

Evolocumab – Repatha

- Data in patients with homozygous familial hypercholesterolemia (HoFH):
- A multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 49 patients (not on lipid-apheresis therapy) with homozygous familial hypercholesterolemia (HoFH). In this trial, 33 patients received subcutaneous injections of 420 mg of evolocumab once monthly and 16 patients received placebo as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe).

Evolocumab – Repatha

- Characteristics of the HoFH patients included:
 - The mean age at baseline was 31 years, 49% were women, 90% White, 4% were Asian, and 6% other. The trial included 10 adolescents (ages 13 to 17 years), 7 of whom received evolocumab. The mean LDL-C at baseline was 349 mg/dL with all patients on statins (atorvastatin or rosuvastatin) and 92% on ezetimibe. The diagnosis of HoFH was made by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration > 500 mg/dL together with either xanthoma before 10 years of age or evidence of HeFH in both parents.

Evolocumab – Repatha

- Results after 12 weeks:
 - In these patients with HoFH, the **difference between evolocumab and placebo in mean percent change in LDL-C from baseline to Week 12 was -31% (95%CI: -44%, -18%; p < 0.0001).**
 - **Patients known to have two LDL-receptor negative alleles (little to no residual function) did not respond to evolocumab.**

Evolocumab – Repatha OSLER 1 & 2 Trials

- **The rate of cardiovascular events at 1 year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio in the evolocumab group, 0.47; 95% confidence interval, 0.28 to 0.78; P=0.003).**
 - N Engl J Med 2015; 372:1500-1509

Flibanserin – Addyi by Sprout/Valeant

- **August 18, 2015 Flibanserin (Addyi) was FDA approved for: Treatment of hypoactive sexual desire disorder in premenopausal women (HSDD)**
- **Dosing regimen: 100 mg tablet orally once daily at bedtime Cost: ~ \$850.00/30 tabs**
 - administration during waking hours increases the risks of hypotension, syncope, accidental injury, and central nervous system (CNS) depression (such as somnolence and sedation).
 - Discontinue flibanserin after 8 weeks if the patient does not report an improvement in her symptoms.

Flibanserin - Addyi

- June 4, 2015 the FDA Advisory Committees: Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management (DSaRM) **Advisory Committee voted 18 to 6 to recommend FDA approval for the treatment of hypoactive sexual desire disorder in premenopausal women.**
- **Several committee members said they voted “yes” with great misgivings because of the drug’s modest benefit and possible side effects.** “The unmet need seems to be so strong that even for a drug with rather modest benefit, I think approving the product with strong limitations seems to be the right step at this point.”

Flibanserin - Addyi

- **Flibanserin is a new molecular entity that is an agonist at the 5 hydroxytryptamine (5HT) type 1A receptor and an antagonist at the 5HT type 2A receptor. Flibanserin is not approved in any country.**
- First evaluated for the treatment of MDD based upon effects on 5HT but it was not found to be effective and the research switched to HSDD.

Flibanserin - Addyi

- **Hypoactive sexual desire disorder (HSDD) is defined in the DSM IV as “Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician taking into account factors that affect sexual functioning, such as age and the context of the person’s life.”**
 - Occurs in about 7% of premenopausal females.
- The disturbance causes marked distress and interpersonal difficulty.
- The sexual dysfunction is not better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Flibanserin - Addyi

Adverse Effect	Placebo (%) N=1905	Flibanserin 100 mg (%) N= 1543
Dizziness	2.2	11.4
Somnolence	.1	11.2
Nausea	3.7	10.4
Fatigue	5.0	9.2
Insomnia	2.4	4.9
Dry mouth	0.9	2.4
Anxiety	0.9	1.8
Constipation	0.5	1.6
Abdominal pain	0.8	1.5
Sedation	0.2	1.3
Somnolence or sedation or fatigue (CNS depression)	7.9	20.6

Flibanserin - Addyi

- **ADDYI REMS Program ADDYI is available only through a restricted program under a REMS called the ADDYI REMS Program, because of the increased risk of severe hypotension and syncope due to an interaction between ADDYI and alcohol.** Notable requirements of the ADDYI REMS Program include the following:
 - Prescribers must be certified with the program by enrolling and completing training.
 - Pharmacies must be certified with the program and must only dispense to patients pursuant to a prescription from a certified prescriber

Extended Release Aspirin – Durlaza

- Limited data suggests that the **pharmacodynamic effect of Durlaza 162.5 mg is similar to IR aspirin 81 mg.**
- “The mean inhibition of TXB₂ following Durlaza (82%) is lower when compared to IR aspirin 81 mg (93%) after the first dose, but upon repeat administration, near maximal inhibition of serum TXB₂ is achieved, similar to what is achieved following repeated daily doses of IR aspirin.”

Narcan Nasal Spray by Adapt Pharma

- November 18, 2015 the FDA granted fast-track designation and priority review for Narcan nasal spray
- **Administering the drug in one nostril delivered approximately the same levels or higher of naloxone as a single dose of an FDA-approved naloxone intramuscular injection, and achieved these levels in approximately the same time frame.**
- Cost: ~\$37.50/dose



EVZIO (Naloxone) Auto-Injector



Each dose is 0.4mg of naloxone/0.4 ml (IM or SC)
 Only comes in boxes of two single dose auto-injectors plus a training auto-injector that may be reused
 Cost ~\$585.00 for one trainer and two active auto injectors

Respiratory Depression

- Depression of the medullary respiratory center
- Decreased tidal volume and minute ventilation and right-shifted CO₂ response
- Hypercapnea, hypoxia and decreased oxygen saturation
- Immediately life threatening
- Respiratory depression may occur when initial opioid doses are too high, opioids are titrated too rapidly, or opioids are combined with other drugs that are associated with respiratory depression or that may potentiate opioid-induced respiratory depression (such as benzodiazepines).
 - Patients with sleep apnea or other underlying pulmonary conditions may be at higher risk for respiratory depression and opioids should be initiated and titrated carefully.
 - Watch for unusually loud snoring, decreased respirations (less than 8 per minute), and decreased arousal.
 - Sedation occurs before significant respiratory depression and therefore is a warning sign

Who do you consider for Naloxone?

- Consider naloxone for patients with risk factors for overdose (e.g., high dose, switching from one opioid to another, history of overdose or substance abuse, etc).
- There is no “safe” opioid dose, but daily dosages of 50 to <100 mg oral morphine or its equivalent increase the risk of opioid overdose by about two- to five-fold compared to daily dosages of <20 mg morphine or its equivalent. Daily dosages of >100 mg morphine or its equivalent are associated with a two- to almost nine-fold higher risk compared to daily dosages of <20 mg of morphine or its equivalent
