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.
Zoster Vaccine

• The Long-term persistence sub-study (LTPS) enrolled 6867 SPS vaccine recipients. Compared to SPS, estimated vaccine efficacy in LTPS decreased from 61.1% to 37.3% for the herpes zoster (HZ) burden of illness (BOI), from 66.5% to 35.4% for incidence of postherpetic neuralgia, and from 51.3% to 21.1% for incidence of HZ, and declined for all 3 outcome measures from 7 through 11 years post-vaccination. Vaccine efficacy for the HZ BOI was significantly greater than zero through year 10 post-vaccination, whereas vaccine efficacy for incidence of HZ was significantly greater than zero only through year 8.

  – Clinical Infectious Diseases 2014; 60: 900-909
Immunization Update – New Zoster sub-unit Vaccine – Shingrix By GSK

• GSK reported the initial results of ZOE-50 a randomized, observer-blind, placebo-controlled, multi-center, multinational phase III efficacy study designed to assess HZ/su (herpes zoster/sub-unit vaccine) in 16,160 patients age 50 and older.
  – viral protein (gE) combined with the adjuvant system - AS01B (a liposome-based adjuvant system containing immunoenhancers) (Not a live attenuated vaccine)
  – 2-dose schedule at 0 and 2 months.
  – The vaccine efficacy (defined as the reduction in disease incidence in the vaccinated group compared to the unvaccinated group) in adults 50 years and older was 97.2%, compared to placebo.
    • Study 110390. 2014. Available at: http://www.gsk-clinicalstudyregister.com/ *
HZ/su (herpes zoster/sub-unit vaccine) - Shingrix

- In ZOE-70, 13,900 participants who could be evaluated (mean age, 75.6 years) received either HZ/su (6950 participants) or placebo (6950 participants). During a mean follow-up period of 3.7 years, herpes zoster occurred in 23 HZ/su recipients and in 223 placebo recipients (0.9 vs. 9.2 per 1000 person-years). Vaccine efficacy against herpes zoster was 89.8% (95% confidence interval [CI], 84.2 to 93.7; P<0.001) and was similar in participants 70 to 79 years of age (90.0%) and participants 80 years of age or older (89.1%).
  - GSK has filed with the FDA for approval on Oct 24, 2016
• Fluzone High-Dose was 24.2% more effective in preventing influenza in 32,000 adults aged 65 years or older than regular Fluzone in a large-scale 2 year clinical trial conducted in the US and Canada, vaccine maker Sanofi Pasteur told the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention today.

• The rate of laboratory-confirmed influenza among participants receiving Fluzone High-Dose was 1.43% compared with 1.89% among patients immunized with Fluzone. For the FDA to deem Fluzone High-Dose as superior, the vaccine needed to demonstrate a relative efficacy rate of at least 9.1%. It achieved a rate more than twice that — \( RRR=24.2\%, \quad ARR = 0.46\%, \quad NNT = 218 \)
Influenza Positive Tests Reported to CDC by Public Health Laboratories, National Summary, 2016-17 Season, week ending Feb 11, 2017
Reported by: U.S. WHO/NREVSS Collaborating Laboratories

- **Cumulative**
- **Most recent 3 weeks**
  Number of Influenza Positive Tests
  - A (H1) - 0
  - A (Unable to Subtype) - 0
  - A (H3) - 16687
  - A (H1N1)pdm09 - 414
  - A (Subtyping not Performed) - 288
  - B (Lineage Unspecified) - 365
  - H3N2v - 0
  - B (Victoria Lineage) - 533
  - B (Yamagata Lineage) - 678
  - No Data
2016-17 Influenza Season Week 13 ending Apr 01, 2017

ILI Activity Level

- **High**
- **Moderate**
- **Low**
- **Minimal**
- **Insufficient Data**

*This map uses the proportion of outpatient visits to healthcare providers for influenza-like illness to measure the ILI activity level within a state. It does not, however, measure the extent of geographic spread of flu within a state. Therefore, outbreaks occurring in a single city could cause the state to display high activity levels.*

*Data collected in ILINet may disproportionately represent certain populations within a state, and therefore may not accurately depict the full picture of influenza activity for the whole state.*

*Data displayed in this map are based on data collected in ILINet, whereas the State and Territorial flu activity map are based on reports from state and territorial epidemiologists. The data presented in this map is preliminary and may change as more data is received.*

*Differences in the data presented by CDC and state health departments likely represent differing levels of data completeness with data presented by the state likely being the more complete.*

*For the data download you can use Activity Level for the number and Activity Level Label for the text description.*
Antiviral Resistance of Influenza Viruses

• The WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza at CDC tested 807 influenza virus specimens (94 influenza A (H1N1)pdm09, 519 influenza A (H3N2), and 194 influenza B viruses) collected in the United States from October 1, 2016, through February 4, 2017, for resistance to the influenza neuraminidase inhibitor antiviral medications oseltamivir, zanamivir, and peramivir, drugs currently approved for use against seasonal influenza. All 807 influenza viruses tested were found to be sensitive to all three antiviral medications. An additional 114 influenza A (H3N2) viruses were tested for resistance to oseltamivir and zanamivir, and were found to be sensitive to both antiviral medications.

• MMWR February 17, 2017 / 66(6);159–166
2016-2017 Influenza Vaccine Effectiveness

• Interim estimates of vaccine effectiveness based on data collected from November 28, 2016, through February 4, 2017, indicate that overall the influenza vaccine has been 48% (95% confidence interval [CI] = 37%–57%) effective in preventing influenza-related medical visits across all age groups, and specifically was 43% (CI = 29%–54%) and 73% (CI = 54%–84%) effective in preventing medical visits associated with influenza A (H3N2) and influenza B, respectively.

• Most influenza infections this season have been caused by influenza A (H3N2). This virus poses "special challenges," they said, because it undergoes more frequent and extensive genetic changes than either the H1N1 A or influenza B strains. Because of this, it requires more frequent vaccine updates to "maintain activity against evolving circulating strains."

• This year's flu shot has been most effective against H3N2 A viruses among children ages 6 months to 8 years (vaccine effectiveness 53%, 95% CI 16%–74%) and adults 50-64 years old (50%, 95% CI 23%-67%).
  • MMWR February 17, 2017 / 66(6);159–166
CDC who has received Flu Vaccine this year?

- Children 6 months thru 17 years of age: 37%
- People age 18 thru 64 years of age: 37%
- People age 65 and older: 57%
- Pregnant women: 47%
  – MMWR Feb 17, 2017
Tdap in Pregnancy Update 2017

• The recommendation to vaccinate mothers, including adolescent mothers, as early as possible in the 27- to 36-week gestational window. The words "as early as possible" were added because evidence shows that when the immunization is given closer to 27 weeks, "the baby is born with a higher concentration of maternal antibodies.

• The most severe complications for pertussis occur in the first 2 months of a child's life, yet infants cannot receive the pertussis vaccine before 2 months of age.

  – MMWR February 10, 2017 / 66(5);136–138
Hepatitis B Vaccine 2017

• Adults with chronic liver disease, including, but not limited to, hepatitis C virus infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level greater than twice the upper limit of normal should receive a HepB series.

  – MMWR February 10, 2017 / 66(5);136–138
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: $15.00 per day or $435.00/mo
GoodRx.com
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


• 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.
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/LOE 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”

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)

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.

Available as a scored 5 mg tablet and 7.5 mg unscored tablet
Cost is reported to be ~$440.00 per month
Ivabradine – Corlanor

SHIFT Trial

- The Systolic Heart failure treatment with the If 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.
  - Lancet Volume 376, No. 9744, p875–885, 11 September 2010
Ivabradine – Corlanor

• All subjects were initiated on ivabradine 5 mg (or matching placebo) twice daily and the dose was increased to 7.5 mg twice daily or decreased to 2.5 mg twice daily to maintain the resting heart rate between 50 and 60 bpm, as tolerated.

• The primary endpoint was a composite of the first occurrence of either hospitalization for worsening heart failure or cardiovascular death.
  – 89% of patients were taking beta-blockers, with 26% on guideline-defined target daily doses. The main reasons for not receiving the target beta-blocker doses at baseline were hypotension (45% of patients not at target), fatigue (32%), dyspnea (14%), dizziness (12%), history of cardiac decompensation (9%), and bradycardia (6%).
  – 91% of patients were taking either an ACEI or ARB
  – 83% of patients were taking diuretics and 60% aldosterone antagonists
# Ivabradine – Corlanor

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ivabradine</th>
<th>Placebo</th>
<th>HR 95% CI</th>
<th>P-value</th>
<th>ARR/NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite of time to first hospitalization for HF and CV death</td>
<td>793 (24.5%)</td>
<td>937 (28.7%)</td>
<td>0.82 (0.75-0.90)</td>
<td>&lt;0.0001</td>
<td>4.2%/24</td>
</tr>
<tr>
<td>Hospitalization for worsening HF</td>
<td>505 (15.6%)</td>
<td>660 (20.2%)</td>
<td>0.74 (0.66-0.83)</td>
<td>&lt;0.0001</td>
<td>4.6%/24</td>
</tr>
<tr>
<td>CV death as first event</td>
<td>288 (8.9%)</td>
<td>277 (8.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- FDA Watch List 12-2016
  - FDA has received reports of ventricular arrhythmias in patients taking ivabradine from the FDA Adverse Events Reporting System (FAERS) and is evaluating the need for regulatory action.
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)
Auvi-Q Auto-injector

Kaleo, Auvi-Q’s manufacturer, will charge patients who have commercial insurance $0 for the product, whether or not the insurance company pays for it. It will also give the product away to families with an income of less than $100,000. For those paying cash who do not qualify to get Auvi-Q for free, the product will cost $360. But the list price for Auvi-Q, and the starting point for insurance companies, will be much higher: $4,500,
Adrenaclick Brand

Adrenaclick Brand 2 pack by Amedra the cost is ~ $480.00 for both the 0.15 and 0.3 mg auto-injectors
AdrenaClick

carrying case

end cap  auto-injector  viewing window  red tip  end cap
Generic Adrenacllick

Generic Adrenacllick auto-injector 2 pack by Amedra now Impax in both 0.15 and 0.3 mg ~ $109.99 at CVS up to ~ $400.00 at other pharmacies
EpiPen Brand by Mylan 2 Pack both 0.15 (EpiPen Jr) and 0.3 mg costs ~ $635.00
Generic EpiPen

Generic EpiPen by Mylan costs ~ $300.00 per 2 pack of both the 0.15 and 0.3 mg auto-injectors
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
- 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 RESPICCLICK (albuterol sulfate) inhalation powder
PROAIR RESPICLINK (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 RESPICLINK inhaler is now ready to use.
- Do not open the cap unless you are taking a dose.
Fluticasone propionate /Salmeterol inhalation powder AirDuo RespiClick

• FDA approved 1-27-2017 for the treatment of asthma in patients aged 12 years and older (one inhalation twice a day).

• Inhalation Powder containing fluticasone propionate 55 mcg, 113 mcg, or 232 mcg and salmeterol (14 mcg) per actuation.

• Class label “Asthma Related Death” as with all LABA’s

• Teva has not announced a launch date or price to date
Fluticasone propionate /Salmeterol inhalation powder AirDuo RespiClick

- Fluticasone propionate/salmeterol xinafoate MDPI 118/13.2 mcg had similar clinical efficacy with lower systemic exposure when compared to the 50 mcg of salmeterol in fluticasone propionate/salmeterol 100/50 mcg dry powder inhaler
- AirDuo RespiClick has a yellow cap

- Instruct patients to not open their inhaler unless they are taking a dose. Repeated opening and closing the cover without taking medication will waste medication and may damage the inhaler.
- Advise patients to keep their inhaler dry and clean at all times. Never wash or put any part of the inhaler in water.
Fluticasone propionate /Salmeterol inhalation powder AirDuo RespiClick by Teva

• Teva's version of GSK's blockbuster medicine, called AirDuo RespiClick, is not directly substitutable for Advair and is only approved for asthma, while Advair is also widely used for chronic obstructive pulmonary disease (COPD).
  – Teva's product promises to grab some of this business in asthma but the bigger threat will come from fully substitutable generic copies of Advair, which are still pending approval.
  – The U.S. Food and Drug Administration is due to decide whether to approve the first of these, from Mylan, by March 28. A rival version from Hikma and Vectura is close behind, with an approval date of May 10.
Fluticasone propionate - ArmonAir RespiClick by Teva

FDA approved for maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.

Available in 3 strengths 55mcg; 113mcg; and 232mcg of fluticasone propionate as a dry powder inhaler

- The ArmonAir RespiClick inhaler has a dose counter attached to the actuator. Each device contains 60 doses.

- Dose is one inhalation BID
  - Discard the inhaler when the counter displays 0, 30 days after opening the foil pouch or after the expiration date on the product, whichever comes first.
  - Instruct patients to not open their inhaler unless they are taking a dose. Repeated opening and closing the cover without taking medication will waste medication and may damage the inhaler.
  - Advise patients to keep their inhaler dry and clean at all times. Never wash or put any part of the inhaler in water.
Tiotropium – Spiriva Respimat 1.25 mcg/inhalation for Asthma

- September 16, 2015 the FDA approved Spiriva Respimat for the long-term, once-daily, prescription maintenance treatment of asthma in people ages 12 and older. It is not a treatment for sudden asthma symptoms.
- Blue cap color is for patients with asthma!
- Tiotropium 1.25 µg/puff (2 puff/dose or 2.5 mcg) is a long-term, once-daily, prescription maintenance treatment of asthma for people 12 years and older.
- Feb 2017 FDA approved down to age 6 years
**High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)**

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40†)–80 mg</strong>&lt;br&gt;<strong>Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg</strong>&lt;br&gt;<strong>Rosuvastatin (5) 10 mg</strong>&lt;br&gt;<strong>Simvastatin 20–40 mg‡</strong>&lt;br&gt;<strong>Pravastatin 40 (80) mg</strong>&lt;br&gt;<strong>Lovastatin 40 mg</strong>&lt;br&gt;<strong>Fluvastatin XL 80 mg</strong>&lt;br&gt;<strong>Fluvastatin 40 mg bid</strong>&lt;br&gt;<strong>Pitavastatin 2–4 mg</strong></td>
<td><strong>Simvastatin 10 mg</strong>&lt;br&gt;<strong>Pravastatin 10–20 mg</strong>&lt;br&gt;<strong>Lovastatin 20 mg</strong>&lt;br&gt;<strong>Fluvastatin 20–40 mg</strong>&lt;br&gt;<strong>Pitavastatin 1 mg</strong></td>
</tr>
</tbody>
</table>

Specific statins and doses are noted in bold that were evaluated in RCTs. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in italics.
**PCSK9 Loss-of-Function Mutations Resulted in Low LDL-C Levels and Reduced CHD Rates**

- Wild-type PCSK9 degrades LDL receptors\(^b\)\(^c\)
- Loss-of-function mutations increase hepatic *LDLR* expression, reducing LDL-C levels by 15%-40%\(^a\)\(^c\)
- CHD was reduced 47%-88% in *PCSK9* loss-of-function mutation carriers compared with normal individuals\(^a\)

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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
• The ODYSSEY Long Term Trial, 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.

• 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).
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.

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 injection takes ~ 9 minutes. 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

- The Pushtronex system became 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 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

• 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.
Amgen Announces Repatha® (Evolocumab) Significantly Reduced The Risk Of Cardiovascular Events In FOURIER Outcomes Study

- FOURIER (Further Cardiovascular OUtcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) is a multinational Phase 3 double-blind, randomized, placebo-controlled trial in approximately 27,500 patients who had either an MI, an ischemic stroke or symptomatic peripheral artery disease and an LDL ≥70 mg/dL or a non-HDL-C ≥100 mg/dL on optimized statin therapy. Optimized statin therapy was defined as at least atorvastatin 20 mg or equivalent daily with a recommendation for at least atorvastatin 40 mg or equivalent daily where approved. Patients were randomized to receive Repatha subcutaneous 140 mg every two weeks or 420 mg monthly or placebo subcutaneous every two weeks or monthly. The study continued until at least 1,630 patients experienced a key secondary MACE (major adverse cardiac event) endpoint of cardiovascular death, MI or stroke, whichever occurred first. Results will be presented at the American College of Cardiology (ACC) 66th Annual Scientific Session Late-Breaking Clinical Trials session in Washington, D.C. on Friday, March 17 at 8 a.m. ET.
Cognition Sub-Study from FOURIER Trial

• EBBINGHAUS (Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in high cardiovascUlar risk Subjects) is a double-blind, placebo-controlled randomized non-inferiority trial involving approximately 1,900 patients enrolled in the FOURIER outcomes study. Executive function (Spatial Working Memory strategy index primary endpoint) and secondary endpoints of working memory, memory function, and psychomotor speed were assessed using a tablet-based tool (CANTAB) at baseline and select time points.

• The EBBINGHAUS cognitive function trial conducted in FOURIER patients also achieved its primary endpoint, demonstrating that Repatha was non-inferior to placebo for the effect on cognitive function.

Results from the Repatha EBBINGHAUS cognitive function trial will be presented at the Late-Breaking Clinical Trials session on Saturday, March 18 at 8 a.m. ET.
Extended Release Aspirin – Durlaza
by New Haven Pharm

• Sept 2015 FDA approved to:
  – 1. Reduce the risk of death and myocardial infarction (MI) in patients with chronic coronary artery disease, such as patients with a history of MI or unstable angina pectoris or with chronic stable angina
  – 2. Reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or transient ischemic attack

• Dose is 162.5 mg caps taken once a day
  – To be taken 2 hours before or 1 hour after consuming alcohol and must be swallowed whole (Do Not crush or chew)
  – Cost ~ $190.00/30 tabs GoodRx.com
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 TBX2 is achieved, similar to what is achieved following repeated daily doses of IR aspirin.”
Aspirin/omeprazole 81mg-40mg and 325mg-40mg tablets - Yosprala by Aralez

- Indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers
- Cost: $180.00 per 30 tablets
- Generic omeprazole 40 mg $10-15.00/30
# USPSTF Recommendations 2016

## Aspirin Use Recommendations

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Balance of Benefits &amp; Harms for aspirin use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult aged 50 to 59 yrs with a &gt;10% 10-yr CVD risk*</td>
<td>Initiate low-dose aspirin use.</td>
<td>The benefit outweigh the risk for bleeding by a moderate amount</td>
</tr>
<tr>
<td>Adult aged 60 to 69 yrs with a &gt;10% 10-yr CVD risk</td>
<td>The decision to initiate low-dose aspirin use an individual one</td>
<td>The benefit outweigh the risk for bleeding by a small amount</td>
</tr>
<tr>
<td>Adults &lt;50 yrs</td>
<td>No recommendation</td>
<td>The evidence is insufficient &amp; the balance of benefit and harms cannot be determined</td>
</tr>
<tr>
<td>Adults aged &gt;70 yrs</td>
<td>No recommendation</td>
<td></td>
</tr>
</tbody>
</table>

*The USPSTF used a calculator derived from the ACC/AHA pooled cohort equation to predict 10-yr risk for first ASCVD event
USPSTF = U.S. Preventive Services Task Force

http://www.uspreventiveservicestaskforce.org/uspstf/uspsasmi.htm
Aspirin for Primary Prevention in Patients With Diabetes
ADA 2016 Recommendations

- Consider aspirin (75—162 mg/day) for primary prevention in patients at increased risk
  - 10-year risk >10%
  - Includes men and women >50 years who have at least one additional major risk factor
- Aspirin should not be recommended for patients at low risk
  - 10-year risk <5%
  - Includes men and women <50 years with no major additional CVD risk factors
- Clinical judgment is required for patients with 10-year risk of 5% to 10%

Nitroglycerin sublingual powder - GoNitro by Espero

• A sublingual nitroglycerin powder packet available for acute angina and angina prophylaxis. May be used prophylactically 5 to 10 minutes prior to engaging in activities that might precipitate an acute attack. (FDA approved 6/2016)

• In a small controlled study with healthy volunteers, GoNitro bioavailability was on average 45% higher than that of nitroglycerin sublingual spray, and reached the same plasma concentration 96 seconds faster. Clinical significance?
  – GoNitro has a “cool minty taste” and is stable in the foil packet for up to 24 months after manufacturing date.
Nitroglycerin sublingual powder - GoNitro

Dose/Instructions: (0.4 mg/foil packet)

• Step 1. Hold the packet of GONITRO upright with the notch and red arrow line at the top of the packet.

• Step 2. Tap the bottom of the GONITRO packet so that the powder settles at the bottom of the packet.

• Step 3. Hold the GONITRO packet at the notch. Hold the packet as close to your mouth as possible and tear along the red arrow line.

• Step 4. Lift up your tongue.

• Step 5. Pour all of the powder in the GONITRO packet under your tongue.

• Step 6. Close your mouth right away and breathe normally through your nose. Allow all of the powder to dissolve before you swallow. Do not rinse your mouth or spit for 5 minutes after taking GONITRO.

• Step 7. If another dose of GONITRO is needed, repeat Steps 1 through 6.
  – you may take 1 additional packet of GONITRO every 5 minutes, if needed. • You should not take more than 3 packets of GONITRO within 15 minutes. • Get emergency medical help right away if you still have chest pain after taking a total of 3 packets of GONITRO.
Nitroglycerin sublingual powder - GoNitro

Availability/Price:

- GoNitro 400 mcg packets: 36 packets ~ $272.00
- NitroStat 400 mcg SL tablets: 25 tabs ~$30.00
- NitroLingual 400 mcg/Spray (Brand): ~$300.00/60 sprays
- NitroLingual 400 mcg/Spray (Generic): $74.00 - $250.00
- NitroMist 400 mcg/Spray ~$445.00/90 sprays

- Prices from GoodRx.com 11-24-2016
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: ~$140.00 per 2 dose package
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 ~$4500.00 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
SC Board of Medical Examiners and Board of Pharmacy Joint Naloxone Protocol 11/17/2016

Eligible Patients:

- Persons who voluntarily request Naloxone and are at risk of experiencing opioid-related overdose, including but not limited to:
  - Current illicit or non-medical opioid users or persons with a history of such use;
  - Persons with a history of opioid intoxication or overdose and/or emergency medical care for acute opioid poisoning;
  - Persons with an opioid prescription, especially those who have:
    - Known or suspected concurrent alcohol abuse;
    - COPD or other respiratory illness or obstruction or currently smoke;
    - Renal dysfunction, Hepatic disease, cardiac disease, or HIV/AIDS;
    - Concurrent Benzodiazepine prescription;
• Persons from an opioid detoxification and mandatory abstinence program;
• Persons entering methadone maintenance treatment programs (for addiction or pain);
• Persons who may have difficulty accessing emergency medical services; and/or
• Persons who voluntarily request Naloxone and are the caregiver of a person at risk of experiencing an opioid overdose
SC Board of Medical Examiners and Board of Pharmacy Joint Naloxone Protocol 11/17/2016

• Naloxone intranasal preferred but IM also covered
  – Nasal Naloxone HCl 1mg/mL Inj. 2x2mL as pre-filled Luer-Lock syringes (Dispense 2 doses x Intranasal Mucosal Atomizing Devices (MAD 300) or Narcan Nasal Spray
  – IM Naloxone HCl 0.4mg/mL Inj. 2x1mL single dose vials (Dispense 2 doises x intramuscular syringe, 3mL, 25G, 1 inch
  – May be refilled PRN

• Patient Education: Every person dispensed Naloxone shall receive education regarding the risk factors of overdose, signs of an overdose, overdose response steps, and the use of Naloxone. See http://www.naloxonesavesSC.org
SC Board of Medical Examiners and Board of Pharmacy Joint Naloxone Protocol 11/17/2016

• Education components:
  – What is naloxone
  – Who should use naloxone
  – Steps in appropriate use:
    • Identify overdose
    • Call 911
    • Give naloxone
    • Begin CPR
    • Stay until help arrives
    • Place person in recovery position
SC Board of Medical Examiners and Board of Pharmacy Joint Naloxone Protocol 11/17/2016

• Pharmacies choosing to participate in the Naloxone distribution may notify the SC Board of Pharmacy when initiating their participation. See http://www.naloxonesavesSC.org and pharmacists must be able to educate patients/caregivers in the proper use of naloxone.

• Required documentation:
  – A current copy of the Joint Protocol
  – Notice of Informed Consent and Affirmation of Naloxone Purchaser
  – Notice to Primary Care Provider, if identified,
  – All pertinent patient records relative to dispensing of Naloxone HCl without a prescription, must be maintained for a period of 2 years