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

March 24, 2011 FDA approved – Zostavax for patients age 50-59 years

- Compared with placebo, ZOSTAVAX significantly reduced the risk of developing zoster by 69.8% (95% CI [54.1 - 80.6%]) in 22,439 subjects 50 to 59 years of age. Data from the Shingles Prevention Study demonstrated 64% (95% CI 56-71%) efficacy in patients age 60-69 years and 41% (95% CI 28 -52%) efficacy for patients age 70-79 years and. only 18% (95% CI -29 – 48%) efficacy in patients age 80 and above.
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/*
  • NOT FDA APPROVED

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
HZ/su (herpes zoster/sub-unit vaccine) - Shingrix

- The Zoster-048 study was presented 6/21/2017 at the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) meeting.
- The study met its primary objective of demonstrating non-inferior immune response (i.e., antibody concentrations). People who received the zoster vaccine live (ZVL) Zostavax vaccine at least 5 years prior to being vaccinated with Shingrix showed a similar immune response to people without previous exposure to the ZVL vaccine. In addition, Shingrix was well-tolerated in both study groups when assessed up to one month after the second dose of Shingrix.
  — Fierce Pharma 6/22/2017

HZ/su (herpes zoster/sub-unit vaccine) - Shingrix

- CDC medical epidemiologist Dr. Kathleen Dooling said a majority of members of a herpes zoster work group would recommend a preference for GSK's Shingrix over the current vaccine, Merck's Zostavax. That's based on currently available data, Dooling cautioned, adding that the group is awaiting the GSK vaccine’s final price and a cost effectiveness analysis.
- Experts at the ACIP meeting noted that should the FDA approve Shingrix by their October gathering, the group could choose whether to recommend the shot for national vaccination guidelines.
  — Fierce Pharma 6/22/2017

HZ/su (herpes zoster/sub-unit vaccine) - Shingrix

- September 13, 2017 the Vaccines and Related Biological Products Advisory Committee (VRBPAC) of the US Food and Drug Administration (FDA) voted unanimously that the data support the efficacy and safety of Shingrix for the prevention of herpes zoster (shingles) in adults ages 50 and over.
- FDA approval is expected in October 2017
- ACIP Meeting 10/25/2017 vote is on the agenda
HZ/su (herpes zoster/sub-unit vaccine) - Shingrix

- Additional trials are underway in solid and haematological cancer patients, haematopoietic stem cell and renal transplant recipients. These studies will provide additional information on the candidate vaccine’s safety and ability to stimulate immune responses in populations at high risk of shingles because of the weakening of their immune system.
  — Fierce Pharma 6/22/2017

ACIP Meeting 10-25-2013

- 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%, ARR = 0.46%, NNT 218

Adjuvant Flu Vaccine – Flud

by Seqirus Division of Australia’s CSL (Commonwealth Serum Labs founded in 1915)

- Nov 24, 2015 The U.S. Food and Drug Administration approved Flud, the first seasonal influenza vaccine containing an adjuvant. Flud, a trivalent vaccine produced from three influenza virus strains (two subtype A and one type B), is approved for the prevention of seasonal influenza in people 65 years of age and older.
  — Developed and filed by Novartis which sold the influenza vaccine business to CSL in 2015
  — Flud was first approved for use in Italy in 1997 and is currently approved in 38 countries, including Canada and 15 European countries.
**Adjuvant Flu Vaccine – Fluad**

- Fluad, which is manufactured using an egg-based process, is formulated with the adjuvant MF59, an oil-in-water emulsion of squalene oil. Squalene, a naturally occurring substance found in humans, animals and plants, is highly purified for the vaccine manufacturing process.
  
  - Adjuvants are incorporated into some vaccine formulations to enhance or direct the immune response of the vaccinated individual.

**Adjuvant Flu Vaccine – Fluad**

- In individuals 65 years of age and older. In that trial, 7,082 participants received either Fluad or Agriflu. The study showed that Fluad induced antibody levels that were comparable to the levels induced by Agriflu.
- Safety was also evaluated in approximately 27,000 additional individuals 65 years of age and older. No safety concerns were identified with Fluad. The most common adverse events reported include injection site pain and tenderness, muscle aches, headache and fatigue.

**ACIP Meeting 6-22-2016**

- The committee has recommended against any use of the nasal vaccine (Flumist) for the upcoming season. (Also during June 2017 ACIP Meeting)
- The ACIP weighed “data showing poor or relatively lower effectiveness” from three previous flu seasons. In late May, the body received data showing that Flumist was just 3% effective in children aged 2 to 17 during the 2015-2016 flu season, compared with an estimated 63% effectiveness for flu shots. ACIP said “no protective benefit could be measured” from the nasal vaccine.
- The committee voted (13 yes, 1 no, 1 abstain for conflict of interest) to remove LAIV from the Vaccines for Children (VFC) program. The IIV component of the program will not be changed.
New Option for Flu Vaccine in Young Children for 2016-17

- GSK announced Nov 18, 2016 that the FDA had approved Flulaval® Quadrivalent (Influenza Vaccine) to include use in children 6 months and older. (previously approved for age 3 and older)
- This means that both Fluzone and Flulaval can be used in children 6 months of age and older

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
Influenza Vaccine Effectiveness Over Time?

- The CDC examined the association between influenza VE and time since vaccination among patients ≥9 years old with medically attended acute respiratory illness in the US Influenza Vaccine Effectiveness Network using data pooled from the 2011–2012 through 2014–2015 influenza seasons. We used multivariate logistic regression with polymerase chain reaction–confirmed influenza infection as the outcome and vaccination status defined by days between vaccination and symptom onset as the predictor. Models were adjusted for calendar time and other potential confounding factors.

- Results. We observed decreasing VE with increasing time since vaccination for influenza A(H3N2) (P = .004), influenza A(H1N1)pdm09 (P = .01), and influenza B viruses (P = .04).

- Maximum VE was observed shortly after vaccination, followed by a decline in VE of about 7% (absolute) per month for influenza A(H3N2) and influenza B and 6%–11% per month for influenza A(H1N1)pdm09 viruses. VE remained greater than zero for at least 6 months for influenza A(H1N1)pdm09 and influenza B and at least 5 months for influenza A(H3N2) viruses.

- Decline in VE was more pronounced among patients with prior-season influenza vaccination. A similar pattern of increasing influenza risk with increasing time since vaccination was seen in analyses limited to vaccinees.

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

HPV9 Vaccine – Gardasil-9 by Merck

- December 10, 2014 The FDA approved nine-valent HPV vaccine (V503) Gardasil-9 that includes coverage for 6, 11, 16, and 18—just like HPV4—but also for five additional high cancer-risk strains: 31, 33, 45, 52, and 58.

- What might it offer vs. the current vaccines?
  - Additional 25% CIN 2 or cervical lesions
  - Additional 18% vaginal cancer cases
  - Additional 15% cervical cancer cases
  - Additional 4% of oropharyngeal cancer cases

- The FDA has stated that “Gardasil 9 has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal and anal cancers.”
ACIP Meeting 10-19-2016

• The ACIP recommended that 11- to 12-year-olds receive 2 doses of human papillomavirus (HPV) vaccine at least 6 months apart rather than the previously recommended 3 doses to protect against cancers caused by HPV infections. Teens and young adults who start the series later, at ages 15 through 26 years, will continue to need 3 doses of HPV vaccine to protect against cancer-causing HPV infection.

• October 7, 2016, the FDA approved adding a 2-dose schedule for 9-valent HPV vaccine (Gardasil 9) for adolescents aged 9 through 14 years.

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 Update 2017

• New with this schedule is that one dose of the monovalent hepatitis B vaccine is recommended for all newborn children within 24 hours of birth.

— Previously, a birth dose was recommended, but that was interpreted to mean the first couple of weeks of life.

— “There are about 25,000 babies a year born to mothers who are chronically infected with hepatitis B. We know that the risk of transmission to a baby from a mother chronically infected can be as high as 90%. And we know, if babies are infected at birth, they have a significant risk of developing cirrhosis or cancer of the liver.”

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

- The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
- Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months, starting as soon as feasible.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks); administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the first dose. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks.

-- 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

Statin Use for the Primary Prevention of Cardiovascular Disease in Adults by USPSTF 11/2016

- Adults aged 40 to 75 years with no history of CVD, 1 or more CVD risk factors, and a calculated 10-year CVD event risk of 10% or greater.
- The USPSTF recommends that adults without a history of cardiovascular disease (CVD) (ie, symptomatic coronary artery disease or ischemic stroke) use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater.
LDL-C and Atherosclerotic CV Disease: Cause or Surrogate Marker?

- Conclusion: “Consistent evidence from numerous and multiple different types of clinical and genetic studies unequivocally establishes that LDL causes ASCVD.”
- LDL-C should no longer be considered a surrogate marker for ASCVD.

Low-density lipoprotein (LDL) as a causal factor for atherosclerotic cardiovascular disease: key implications

- Cumulative LDL arterial burden is a central determinant for the initiation and progression of atherosclerotic cardiovascular disease.
- The lower the LDL cholesterol (LDL-C) level attained by agents that primarily target LDL receptors, the greater the clinical benefit accrued.
- Both proportional (relative) risk reduction and absolute risk reduction relate to the magnitude of LDL-C reduction.
- Lowering LDL-C in individuals at high cardiovascular risk earlier rather than later appears advisable, especially in those with familial hypercholesterolemia.

AACE 2017 Guidelines

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Treatment goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLC</td>
<td>Non-HDL-C</td>
</tr>
<tr>
<td>Extensive risk</td>
<td>Proaggressive ASCVD including unstable angina in patients after achieving LDL-C &lt;50 mg/dL.</td>
</tr>
<tr>
<td>Very high risk</td>
<td>Established or recent hospitalization for ACS, coronary artery bypass grafting, coronary stenting, 10-year risk ≥20%. Diabetes or CKD G3a with 1 or more risk factors.</td>
</tr>
<tr>
<td>High risk</td>
<td>10-year risk ≥10% and 10-year risk ≥10% with 2 or more risk factors.</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>10-year risk ≥10% and 10-year risk ≥10% with no other risk factors.</td>
</tr>
<tr>
<td>Low risk</td>
<td>Total cholesterol</td>
</tr>
</tbody>
</table>

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ENDOCRINE PRACTICE Vol 23 (Supp 2) April 2017
New FDA Approved Generics

- Ezetimibe 10 mg (Generic Zetia) now FDA approved 12/12/2016 from:
  - Glenmark Pharm Ltd / Par - Endo (First to file 180 day exclusivity)
  - $85.00 - $268.00/30
  - Tea Pharm US - Sandoz - Mylan Pharm Inc.
- Ezetimibe/Simvastatin 10/10, 10/20, 10/40 and 10/80 mg (Generic Vytorin) now FDA approved 4/26/2017 from:
  - Brand 10/40 mg $295.00 - $337.00/30; Generic 10/40 mg $86.00 - $289.00/30
  - Dr. Reddys labs International
  - Impax Labs Inc.
  - Watson Labs Inc.

IMPROVE-IT Trial

- The results of IMPROVE-IT (AHA 11/17/2014 Scientific Sessions). The study included more than 18 000 patients from 39 countries who were stable following ACS (<10 days). Patients were randomized to one of two treatment strategies: simvastatin 40 mg alone or simvastatin 40 mg plus ezetimibe 10 mg. They were followed for a minimum of 2.5 years or until the study investigators accrued 5250 clinical events.
- At baseline, the mean LDL-cholesterol level among the ACS patients was 95 mg/dL in both treatment arms. With simvastatin 40 mg, LDL-cholesterol levels were reduced to 69.9 mg/dL at 1 year. The addition of ezetimibe 10 mg to simvastatin further lowered LDL-cholesterol levels, to 53.2 mg/dL at 1 year. Over 7 years, there remained a significant difference between the two treatments in the achieved LDL-cholesterol levels.

Primary End Point and Individual Components (7-Year Event Rates)

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Simvastatin, n=9077 (%</th>
<th>Ezetimibe/Simvastatin, n=9067 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point (cardiovascular death, MI, unstable angina, coronary revascularization, or stroke)</td>
<td>34.7</td>
<td>32.7</td>
<td>0.016</td>
</tr>
<tr>
<td>All-cause death</td>
<td>15.3</td>
<td>15.4</td>
<td>0.782</td>
</tr>
<tr>
<td>MI</td>
<td>14.8</td>
<td>15.1</td>
<td>0.652</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.4</td>
<td>4.2</td>
<td>0.392</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>4.1</td>
<td>3.9</td>
<td>0.338</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.6</td>
<td>2.1</td>
<td>0.818</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>20.4</td>
<td>21.8</td>
<td>0.107</td>
</tr>
</tbody>
</table>

Primary combined endpoint at 7 years: RRR 6.4%; ARR 2.0%; NNT 50
MI at 7 years: ARR 1.7%; NNT 50
Ischemic stroke at 7 years: 0.7%; NNT 142
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
New FDA Approved Dosing Option

- April 25, 2017 the FDA approved Sanofi and Regeneron's new supplemental Biologics License Application (sBLA) for a once-monthly (every four weeks), 300 mg dose of Praluent® (alirocumab) injection for the treatment of adults with high low-density lipoprotein (LDL) cholesterol. The dose requires 2 injections of 150 mg.
- The once-monthly dose of Praluent was approved by the FDA and the EC based on results from the Phase 3 ODYSSEY CHOICE I study, which evaluated the efficacy and safety of Praluent 300 mg every four weeks compared to placebo in patients with hypercholesterolemia who were or were not also taking concomitant statin.
- Primary Outcome Measures: Percent Change From Baseline in Calculated LDL-C in Participants Not Receiving Concomitant Statin Therapy (N=146) - ITT Analysis [Time Frame: From Baseline to Week 24] as a well as a group receiving statin therapy (N=312).

Odyssey Choice 1 Trial Results

Results: (appear to be similar to the 150 mg every 2 week dose)
- Primary Outcome at 24 weeks in patients (N=144) not taking statins: LDL-C was reduced by 52.7%
- Primary Outcome at 24 weeks in patients (N=308) taking statins: LDL-C was reduced by 58.8%

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.

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 Now we also have Pushtronex System

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

• Data in patients with homozygous familial hypercholesterolemia (HoFH):
  • A multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 49 patients including 10 pts age 13-17 (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., high intensity statins, 92% ezetimibe).
  • Baseline LDL-C mean 349 mg/dl

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.

FOURIER
Further cardiovascular OUTcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

MS Sabatine, RP Giugliano, AC Kaseh, N Honarpour, SM Wasserman, PS Sever, and TR Pedersen,
for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017

N Engl J Med 2017; 376:1713-1722
**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>63 (9)</td>
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<tr>
<td>Male sex (%)</td>
<td>75</td>
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<tr>
<td>Type of cardiovascular disease (%)</td>
<td></td>
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<tr>
<td>Myocardial infarction</td>
<td>81</td>
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<tr>
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<td>19</td>
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<td>Symptomatic PAD</td>
<td>13</td>
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<td>Hypertension</td>
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<td>37</td>
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<td>Current cigarette use</td>
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**Endpoints**

- **Efficacy**
  - Primary: CV death, MI, stroke, hosp. for UA, or coronary revasc
  - Key secondary: CV death, MI or stroke

- **Safety**
  - AEs/SAEs
  - Events of interest incl. muscle-related, new-onset diabetes, neurocognitive
  - Development of anti-evolocumab Ab (binding and neutralizing)

- **TIMI Clinical Events Committee (CEC)**
  - Adjudicated all efficacy endpoints & new-onset diabetes
  - Members unaware of treatment assignment & lipid levels

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</table>
Lipid Lowering Therapy & Lipid Levels at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin use (%)*</td>
<td></td>
</tr>
<tr>
<td>High-intensity</td>
<td>69</td>
</tr>
<tr>
<td>Moderate-intensity</td>
<td>30</td>
</tr>
<tr>
<td>Ezetimibe use (%)</td>
<td>5</td>
</tr>
<tr>
<td>Median lipid measures (IQR) – mg/dL</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>92 (80-109)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>168 (151-189)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44 (37-53)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>153 (100-182)</td>
</tr>
</tbody>
</table>

*Per protocol, patients were to be on atorvastatin ≥20 mg/d or equivalent.
*% were on low intensity or intensity data were missing.
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.

Pooled data; no differences between treatment arms

LDL Cholesterol

50% mean reduction (95% CI 58-60), P<0.00001
Absolute reduction: 56 mg/dl (95% CI 55-57)

Types of CV Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Evolocumab (N=13,784)</th>
<th>Placebo (N=13,780)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr Kaplan-Meier rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD, MI, stroke, UA, or revasc</td>
<td>12.6</td>
<td>14.6</td>
<td>0.85 (0.79-0.92) NNT 50</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>7.3</td>
<td>9.9</td>
<td>0.80 (0.73-0.88) NNT 50</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2.3</td>
<td>2.4</td>
<td>1.09 (0.88-1.35)</td>
</tr>
<tr>
<td>MI</td>
<td>4.4</td>
<td>6.3</td>
<td>0.73 (0.65-0.82) NNT 53</td>
</tr>
<tr>
<td>Hosp for unstable angina</td>
<td>2.2</td>
<td>2.3</td>
<td>0.99 (0.82-1.21)</td>
</tr>
<tr>
<td>Coronary revascular</td>
<td>7.0</td>
<td>9.2</td>
<td>0.89 (0.67-1.21) NNT 46</td>
</tr>
<tr>
<td>Urgent cardiac event</td>
<td>2.7</td>
<td>5.4</td>
<td>0.73 (0.64-0.83)</td>
</tr>
<tr>
<td>Elective cardiac event</td>
<td>2.9</td>
<td>4.6</td>
<td>0.83 (0.73-0.95)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4.8</td>
<td>4.3</td>
<td>1.04 (0.91-1.19)</td>
</tr>
</tbody>
</table>
**Summary for Evolocumab**

- **↓ LDL-C by 59%**
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)
- **↓ CV outcomes in patients already on statin therapy**
  - 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
  - Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  - 25% reduction in CV death, MI, or stroke after 1st year
  - Long-term benefits consistent w/ statins per mmol ↓ LDL-C
- **Safe and well-tolerated**
  - Similar rates of AEs, including DM & neurocog events w/ Evolocumab & placebo
  - Rates of Evolocumab discontinuation low and no greater than placebo
  - No neutralizing antibodies developed

**New Performance-Based Guaranteed Pricing?**

- In March, when cardiovascular outcomes (FOURIER Trial) results were presented for evolocumab (Repatha) at the 66th Scientific Sessions of the American College of Cardiology (ACC), manufacturer Amgen announced a first-of-its-kind offer: the company would pay a refund for all eligible patients who had a heart attack or stroke while taking the cholesterol-fighting injection.
- This week (5-8-2017), Amgen announced that that health services company Harvard Pilgrim has taken the deal. The company, which covers 2.7 million people centered in New England, has signed an outcomes-based contract that some call groundbreaking and others say don’t address the high price of the drug, which lists for more than $14,000 a year but reduces low-density lipoprotein (LDL) cholesterol by 60%.
- At ACC, the results of the FOURIER trial showed that evolocumab reduced the combined risk of heart attack, stroke, and cardiovascular death 15% to 20%, and 25% beyond the first year. No early death reduction in overall deaths were seen.

AJMC.com In Focus Blog 5-7-2017
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.

EBBINGHAUS Cognition Sub-Study

In patients with known cardiovascular disease on background statin followed for 20 months

1. No differences btw evolocumab vs placebo
   - A. A battery of cognitive tests
   - B. Patient-reported everyday cognition
   - C. Adverse cognitive events reported by MD

2. No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL

COPD Treatment: GOLD 2017 Guidelines

- Long-acting bronchodilators. Almost all patients with COPD who experience more than occasional dyspnea should be prescribed long-acting bronchodilator therapy. This could be a long-acting beta agonist (LABA), a long-acting muscarinic antagonist (LAMA), or both. Patients with persistent COPD symptoms while taking one long-acting bronchodilator should be prescribed two (or a combination agent containing two long-acting bronchodilators).
- Inhaled corticosteroids are not recommended as monotherapy in COPD. Combination agents containing inhaled corticosteroids along with long-acting beta agonists are considered appropriate step-up therapy for patients experiencing COPD exacerbations while taking long-acting bronchodilators.
- Oral PDE4 inhibitors are considered an add-on therapy only for patients with COPD with chronic bronchitis and severe airflow restriction who experience COPD exacerbations despite use of a combination bronchodilator with inhaled corticosteroid.
COPD Treatment: GOLD 2017 Guidelines

• Although specific drugs aren’t advised, the GOLD path through Grade B and C (i.e., most of the 11 million people living with COPD in the U.S.) advises dual therapy with a LABA and LAMA.
• Once-daily combination inhalers for COPD will likely result in better adherence, which could result in improved health outcomes compared to twice-daily regimens requiring multiple devices.
• The best inhaler for COPD is the one a patient can afford, understands, agrees with and will use regularly.

Therapeutic Options: Combination Therapy

- An inhaled corticosteroid combined with a long-acting beta₂-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in moderate to very severe COPD.
- Combination therapy is associated with an increased risk of pneumonia.
- Addition of a long-acting beta₂-agonist/inhaled glucocorticosteroid combination to an anticholinergic (tiotropium) appears to provide additional benefits.

Fluticasone furoate /Vilanterol inhalation powder –Breo Ellipta by GSK/Theravance

- Maintenance treatment of COPD: 1 inhalation of Breo Ellipta 100 mcg/25 mcg (fluticasone furoate /vilanterol inhalation powder) once daily.
- Cost ~$310.00 Goodrx.com
- FDA Box Warning as with all other LABA containing medications Asthma Related Deaths but NOT indicated for patients with asthma
Fluticasone furoate /Vilanterol inhalation powder – Breo Ellipta

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

Fluticasone furoate /Vilanterol inhalation powder – Breo Ellipta

- March 19, 2015 the FDA Advisory Committees (Pulmonary, Allergy, Drug safety) voted 16 to 4 to recommend Breo Ellipta for adults 18 y/o and older with asthma but also voted 18-2 against approval for children ages 1-17 y/o.

- The panel also voted 17-3 that the data supported safety in adults but only one panel member voted that safety was supported in children.

ICS/LABA Combination in Children?

- A multicenter trial (VESTRI) randomly assigned 6208 children 4 to 11 years of age who had an asthma exacerbation in the previous year to a combination inhaler with fluticasone propionate (100 mcg or 250 mcg/inhalation) plus salmeterol (Advair) or to monotherapy with fluticasone propionate (100 mcg or 250 mcg/inhalation), one inhalation twice daily for 26 weeks.

- The number of patients who had a severe asthma exacerbation was 25% lower among children who continued taking fluticasone-salmeterol than among those who switched to fluticasone alone.

- Serious adverse events (hospitalization due to asthma exacerbation) occurred in 27 of 3107 patients in the fluticasone-salmeterol group and in 23 of the 3101 patients in the fluticasone group, hazard ratio 1.28 (95% CI 0.73-2.27). No deaths or endotracheal intubations were reported. This hazard ratio suggests that the risk of serious asthma-related events was similar between the two groups.

ICS/LABA Combination in Adults/Adolescents

- **AUSTRI** a multicenter, noninferiority trial, 11,679 adolescents (≥12) and adults with persistent asthma were randomly assigned to take either inhaled fluticasone or the combination of inhaled fluticasone-salmeterol (Advair) for 26 weeks. Combination therapy was administered using a single inhaler that contained both fluticasone and salmeterol.
- The risk of a severe asthma exacerbation was 21% lower in the fluticasone-salmeterol group than in the fluticasone-only group (hazard ratio, 0.79; 95% CI, 0.70 to 0.89).
- The hazard ratio for a serious asthma-related adverse event in the fluticasone-salmeterol group compared with fluticasone alone was 1.03 (95% CI 0.64-1.66), suggesting no increased risk related to the addition of the LABA. Furthermore, no deaths occurred in either group, and no difference was noted in the rate of asthma-related hospitalizations.


ICS/LABA Combination in Adults/Adolescents

- The combination of budesonide (80 mcg or 160 mcg) plus formoterol (Symbicort) was compared with budesonide (80 mcg or 160 mcg) in a multicenter trial of 11,693 patients aged 12 and older with one to four asthma exacerbations in the previous year; 2 inhalations were used twice daily for 26 weeks.
- The risk of an asthma exacerbation was 16 percent lower in the budesonide-formoterol group.
- A serious asthma-related event occurred in 43 of 5846 patients in the combination arm and in 40 of 5847 in the budesonide arm, hazard ratio 1.07 (95% CI 0.70-1.65), suggesting a similar risk between the groups.


Umeclidinium and Vilanterol – Anoro Ellipta Inhaler by GSK/Theravance

Contains two blisters: umecclidinium 62.5 mcg per blister and the other contains vilanterol 25 mcg per blister.

Maintenance treatment of COPD:
1 inhalation once daily

Cost: ~$330.00 / 30 doses GoodRx.com

* FDA Box Warning as with all other LABA containing medications Asthma Related Deaths but NOT indicated for patients with asthma
Umeclidinium – Incruse Ellipta Inhaler
by GSK/Theravance

Contains umeclidinium 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.

Cost ~ $250.00 Goodrx.com

Tiotropium – Spiriva Respimat
2.5 mcg/inhalation for COPD by BI

• FDA approved 9-25-2014; indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).
• The delivered dose is 2.5 microgram tiotropium per puff (2 puffs/dose or 5 mcg) and is equivalent to 3.124 microgram tiotropium bromide monohydrate
• NOTE there are now two different inhalers!
• Cost ~ $350.00 Goodrx.com (both)

Tiotropium – Spiriva Respimat 1.25 mcg/inhalation for Asthma by BI

• 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!
Glycopyrrolate – Seebr Neohaler by Novartis

- Dosed twice a day by inhalation (15.6 mcg / capsule for inhalation)
- Cost: $330.00/60 capsules GoodRx.com

Store SEEBr 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

Store SEEBr 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 Formoterol – Bevespi Aerosphere by A/Z

- April 25, 2016 the FDA approved Bevespi a new LABA/LAMA co-suspension combination pressurized metered dose inhaler (pMDI) for twice a day maintenance therapy in patients with COPD
- Dose 2 inhalations twice a day 120 inhalations per pMDI
- Cost: $362.00/ canister GoodRx.com 1-25-17
  - Prime 4 times prior to initial use, 2 times if not used for a week or more and after weekly rinsing of inhaler (NOT the canister!)
Combination of Glycopyrrolate and Formoterol – Bevespi Aerosphere

- Shake well before each use
- Dose counter on top of canister (declines in 10’s)
- Remove canister weekly and run inhaler device under warm water for 30 sec from both ends weekly to clean inhaler and let dry over night

Tiotropium and Olodaterol - Stiolto Respimat

- 5/21/2015 the FDA approved Boehringer Ingelsheim’s 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 in 7,000 pts - the 52-week replicate TONADO® 1&2 studies and the 6-week cross-over VIVACTIO® dose finding study.

Stiolto Respimat Inhalation Spray: 60 metered actuations
Cost: ~ $325.00

Coming Soon: ICS/LABA/LAMA Combinations

- GSK announced 11/21/16 the filing with the FDA of a once-daily, closed triple combination therapy fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI 100/62.5/25 mcg) for patients with chronic obstructive pulmonary disease (COPD).
- PT010 is a triple-drug combination of the long-acting muscarinic antagonist (LAMA) glycopyrronium, the long acting β2-agonist (LABA) formoterol fumarate and budesonide, an inhaled corticosteroid (ICS) by Pearl (both A/Z and Novartis are working on this combo)
Trelegy Ellipta (fluticasone furoate, umeclidinium, and vilanterol) by GSK/Theravance

Trelegy Ellipta (fluticasone furoate, umeclidinium, and vilanterol)

- FDA approved 9/18/2017 for long-term once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. A triple combination ICS/LAMA/LABA for inhalation.
- FDA Box Warnings: Not indicated for the treatment of asthma and long-acting beta2-adrenergic agonists (LABA), such as vilanterol, increase the risk of asthma-related death.
- Inhalation Powder: Inhaler containing 2 foil blister strips of powder formulation for oral inhalation. One strip contains fluticasone furoate 100 mcg per blister and the other contains umeclidinium/vilanterol 62.5 mcg/25 mcg per blister.

Trelegy Ellipta (fluticasone furoate, umeclidinium, and vilanterol)

- Two confirmatory trials 1 and 2 in 206 patients each: mean age of 64 years, 92% white, 66% male, and an average smoking history of 48 pack-years, with 50% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV1 was 46% (range: 14% to 76%), the mean postbronchodilator FEV1/FVC ratio was 0.48 (range: 0.21 to 0.70), and the mean percent reversibility was 13% (range: 24% to 86%).
- The primary endpoint was change from baseline in trough (predose) FEV1 at Day 85 (defined as the mean of the FEV1 values obtained at 23 and 24 hours after the previous dose on Day 84).
- In both trials, umeclidinium + fluticasone furoate/vilanterol demonstrated a statistically significant increase relative to placebo + fluticasone furoate/vilanterol (mean change in trough FEV1 was 124 and 122 ml at day 85); similar results were demonstrated for the secondary endpoint of the weighted mean FEV1 (0 to 6 hours postdose was 153 and 147 ml on Day 84).
Trelegy Ellipta (fluticasone furoate, umeclidinium, and vilanterol)

- Health-related quality of life was assessed in Trials 1 and 2 using the St. George’s Respiratory Questionnaire (SGRQ).
- In Trial 1, the responder rate (response defined as a decrease in score from baseline of 4 or more) at Day 84 was 40% for umeclidinium 62.5 mcg + fluticasone furoate/vilanterol vs. 35% for placebo + fluticasone furoate/vilanterol (odds ratio 1.2; 95% CI: 0.8, 1.8). N.S.
- In Trial 2, the responder rate was 35% for umeclidinium + fluticasone furoate/vilanterol vs. 21% for placebo + fluticasone furoate/vilanterol (odds ratio 2.0; 95% CI: 1.3, 3.1).

St. George’s Respiratory Questionnaire (SGRQ)

- Disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. The SGRQ has 50 items with 2 parts and 3 components. Part 1: Symptoms component (frequency & severity) with a 1, 3 or 12-month recall (best performance with 3- and 12-month recall); Part 2: Activities that cause or are limited by breathlessness; Impact components (social functioning, psychological disturbances resulting from airways disease) refer to current state as the recall.
- Scale Format: Part I (Symptoms): several scales; Part II (Activity and Impacts): dichotomous (true/false) except last question (4-point Likert scale)
- Administration Technique: self administered
- Scoring and Interpretation: Scores range from 0 to 100, with higher scores indicating more limitations.

LAMA added to ICS/LABA in Patients with COPD

- 1,857 patients were given ICS + LABA + Tio, and 996 were given ICS + LABA. Mean follow-up was 4.65 years. The adjusted HR for all-cause mortality for ICS + LABA + Tio vs ICS + LABA was 0.65 (95% CI, 0.57-0.75; P<.001). Adjusted HRs for hospital admissions and oral corticosteroid bursts were 0.85 (95% CI, 0.73-0.99; P = .04) and 0.71 (95% CI, 0.63-0.80; P<.001), respectively.
- CONCLUSIONS The study suggests that the addition of tiotropium to ICSs and LABA therapy may confer benefits in reducing all-cause mortality, hospital admissions, and oral corticosteroid bursts in patients with COPD.
**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.
  - In a 343 patient placebo controlled trial 100 mcg furoate QD was similar to 250 mcg of fluticasone propionate BID
  - Available in 100 and 200 mcg/inhalation Ellipta dose dry powder inhaler
  - Cost ~ $150.00 per 100 mcg and ~$200.00/200 mcg Goodrx.com

**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).
  - April 29, 2016 now FDA approved for children 4-11 years of age.
  - DO NOT USE with a spacer!
  - 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**

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.
Fluticasone propionate /Salmeterol inhalation powder AirDuo RespiClick by Teva

- 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
- 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).
- Cost for all 3 is ~$90.00/ inhaler vs. Advair 100/50 mcg ~$317.00, 250/50 mcg ~$392.00, 500/50 mcg ~$515.00

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 - ArmonAir RespiClick by Teva

- 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.
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

depend cap  auto-injector viewing window red tip  end cap
**Generic Adrenaclick**
Generic Adrenaclick 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 (K-Mart just announced $200.00)

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**EpiPen Brand**
EpiPen Brand by Mylan 2 Pack both 0.15 (EpiPen Jr) and 0.3 mg costs ~ $635.00

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**Generic EpiPen**
Generic EpiPen by Mylan costs ~ $300.00 per 2 pack of both the 0.15 and 0.3 mg auto-injectors
**Newest Epinephrine Auto-Injector Symjepi**

by Adamis Pharmaceuticals

- **June 15, 2017** The FDA has approved Adamis’ **EPINEPHRINE INJECTION, USP, 1:1000 (0.3 mg Pre-filled single dose syringe)** (“PFS”) for the emergency treatment of allergic reactions (Type I) including anaphylaxis. The FDA has also approved the PFS trade name of Symjepi™.
  - Adamis is preparing to submit a second NDA to the FDA for the junior version of Symjepi.
  - The company believes that the anticipated lower cost, small size and user-friendly design for Symjepi could be an attractive option for a significant portion of both the retail (patient) and non-retail (professional) sectors of the epinephrine market.
  - Should be available second half of 2017.

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**Betrixaban – Bevyxxa by Portola Pharm**

- FDA approved 6/23/2017: **betrixaban** is a factor Xa (FXa) inhibitor indicated for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE. (First oral anticoagulant FDA approved for this indication) Fast Track designation and approved by the FDA under Priority Review.
  - The safety and effectiveness of betrixaban have not been established in patients with prosthetic heart valves because this population has not been studied.

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**Betrixaban – Bevyxxa**

- **Betrixaban is a direct factor Xa inhibitor** anticoagulant. Betrixaban exerts its antithrombotic effect by inhibiting free and prothrombinase-bound factor Xa, an important validated target in the blood coagulation pathway, in a concentration-dependent manner.
  - Peak plasma concentrations occur within 3 to 4 hours after oral administration. The oral bioavailability is 34%. Absorption is affected by fatty food, which decreases both the peak concentration and area under the curve by 50%.
  - The primary route of elimination is hepatobiliary into the gut (82% to 89%). Metabolism by cytochrome P450 enzymes is very low (less than 1%). Renal clearance accounts for 5% to 7% of the dose. The terminal half-life is 37 hours, while the pharmacologic half-life (time to 50% reduction in efficacy) is approximately 20 hours. Protein binding is 60%
Betrixaban – Bevyxxa

• FDA approval is based upon the APEX study, a randomized, double-blind, double-dummy trial vs. enoxaparin in 7,513 patients 40 and older, hospitalized for an acute medical illness, at risk for VTE due to moderate or severe immobility, and had additional risk factors for VTE (> = 75 years old; 60 through 74 years of age with D-dimer ≥ 2 ULN, or 40 through 59 years of age with D-dimer ≥ 2 ULN and a history of either VTE or cancer).

  – Excluded patients whose condition required prolonged anticoagulation (e.g., concurrent VTE, atrial fibrillation, cardiac valve prosthesis), were at increased risk of bleeding, had liver dysfunction, were on dual antiplatelet therapy, or patients who had both severe renal insufficiency (CrCl 15-29 ml/min) and required the concomitant use of a P-gp inhibitor.

  – Expected duration of hospitalization was at least 3 days and patients were expected to be moderately or severely immobilized for at least 24 hours. The causes for hospitalization included heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke.


Initial Summary of Results from APEX Study

Press Release Portolo 2016

<table>
<thead>
<tr>
<th>Primary efficacy analysis (VTE)</th>
<th>Primary safety analysis (major bleeding)†</th>
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<tbody>
<tr>
<td>RR</td>
<td>RR</td>
</tr>
<tr>
<td>P value</td>
<td>P value</td>
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<tr>
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<tr>
<td></td>
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<tr>
<td>Cohort 2: Elevated D-dimer or age ≥75 years</td>
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<tr>
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<td>0.029</td>
</tr>
<tr>
<td>Overall study population</td>
<td>0.760</td>
</tr>
<tr>
<td></td>
<td>0.006</td>
</tr>
</tbody>
</table>

* A p value of <0.05 is accepted as the gold standard for statistical significance.
† No significant difference in major bleeding between any groups.

Betrixaban – Bevyxxa

• Patients were randomized 1:1 to:
  – Betrixaban arm (betrixaban 160 mg orally on Day 1, then 80 mg once daily for 35 to 42 days AND enoxaparin subcutaneous placebo once daily for 6 to 14 days), or
  – Enoxaparin arm (enoxaparin 40 mg subcutaneously once daily for 6 to 14 days AND betrixaban placebo orally once daily for 35 to 42 days).

  – Patients with severe renal impairment (creatinine clearance ≥ 15 and < 30 mL/min) received reduced doses of study medications (Betrixaban 80 mg loading dose, then 40 mg once daily or enoxaparin 20 mg once daily) along with corresponding placebo.

  – Patients taking a concomitant P-gp inhibitor received Betrixaban 80 mg loading dose, then 40 mg once daily or enoxaparin 40 mg subcutaneously once daily for 6 to 14 days along with corresponding placebo.

  – The median duration of treatment was 36 days in the betrixaban group and 9 days in the enoxaparin group.
Betrixaban – Bevyxxa

• Primary End Point(s):
  – Composite of asymptomatic proximal deep vein thrombosis (DVT) between day 32 and day 47, symptomatic proximal or distal DVT, symptomatic nonfatal pulmonary embolism (PE), or death from VTE between days 1 and 42.
  – Efficacy analyses were performed based on the modified Intent-to-Treat (mITT) population (pts who had taken at least 1 dose and had follow-up data on at least 1 efficacy endpoint).


<table>
<thead>
<tr>
<th>Table 5: Efficacy Outcomes in APEX Trial (mITT Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Composite Outcome</td>
</tr>
<tr>
<td>Asymptomatic Event</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
</tr>
<tr>
<td>Nonfatal PE</td>
</tr>
<tr>
<td>VTE-related Death</td>
</tr>
<tr>
<td>Symptomatic Event</td>
</tr>
</tbody>
</table>

1 Percentages and event rates are based on the total number of patients and events included in each treatment group.
2 Relative Risk (Betrixaban/enoxaparin) is based on the Mann-Whitney test stratified by the dosing strategy and D-dimer status from the local laboratory. The analyses are not adjusted for multiplicity.
3 Symptomatic events include symptomatic DVT, nonfatal PE or VTE-related death.

Betrixaban – Bevyxxa

• For patients with D-dimer ≥ 2 ULN at baseline, the event rate is 5.7% in the Betrixaban arm vs. 7.2% in the enoxaparin arm (relative risk = 0.79, 95% CI [0.63, 0.98]), ARR = 1.5%, NNT = 67

• For patients with D-dimer ≥ 2 ULN at baseline or age ≥ 75 years, the event rate is 4.7% in the Betrixaban arm vs. 6.0% in the enoxaparin arm (relative risk = 0.78, 95% CI [0.64, 0.96]), ARR = 1.3%, NNT = 77
Betrixaban – Bevyxxa

Table 6: Efficacy Outcomes in APEX Trial (mITT Population) – Patients Stratified to 80 mg BEVYXXA Dose

<table>
<thead>
<tr>
<th></th>
<th>Betrixaban</th>
<th>Enoxaparin</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Outcome</td>
<td>12 (0.5)</td>
<td>10 (0.7)</td>
<td>1.8 (0.45-6.22)</td>
</tr>
<tr>
<td>Asymptomatic Event</td>
<td>9 (0.4)</td>
<td>7 (0.5)</td>
<td>1.4 (0.4-4.8)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>1 (0.05)</td>
<td>1 (0.05)</td>
<td>1.0 (0.04-2.48)</td>
</tr>
<tr>
<td>Nonfatal PE</td>
<td>5 (0.2)</td>
<td>3 (0.2)</td>
<td>1.6 (0.5-5.0)</td>
</tr>
<tr>
<td>VTE-related Death</td>
<td>1 (0.05)</td>
<td>0.5 (0.02)</td>
<td>0.9 (0.03-2.81)</td>
</tr>
<tr>
<td>Symptomatic Events</td>
<td>11 (0.4)</td>
<td>14 (0.5)</td>
<td>0.79 (0.34, 1.82)</td>
</tr>
</tbody>
</table>

NNT = 50

Table 7: Efficacy Outcomes in APEX Trial (mITT Population) – Patients Stratified to 40 mg BEVYXXA Dose

<table>
<thead>
<tr>
<th></th>
<th>Betrixaban</th>
<th>Enoxaparin</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Outcome</td>
<td>14 (0.5)</td>
<td>12 (0.7)</td>
<td>1.2 (0.48-3.33)</td>
</tr>
<tr>
<td>Asymptomatic Event</td>
<td>10 (0.4)</td>
<td>7 (0.5)</td>
<td>1.4 (0.43-4.83)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>0.5 (0.02)</td>
<td>1 (0.05)</td>
<td>0.5 (0.02-2.73)</td>
</tr>
<tr>
<td>Nonfatal PE</td>
<td>3 (0.1)</td>
<td>2 (0.1)</td>
<td>1.5 (0.5-4.7)</td>
</tr>
<tr>
<td>VTE-related Death</td>
<td>1 (0.05)</td>
<td>0.5 (0.02)</td>
<td>0.9 (0.03-2.8)</td>
</tr>
<tr>
<td>Symptomatic Events</td>
<td>13 (0.5)</td>
<td>16 (0.5)</td>
<td>0.8 (0.34-1.96)</td>
</tr>
</tbody>
</table>

NNT = 167

- Major or clinically relevant nonmajor bleeding occurred in 3.1% of the betrixaban group and 1.6% of the enoxaparin group (RR, 1.97; 95% CI, 1.44 to 2.68; P<0.001), ARI = 1.5%, NNH = 67.
- New ischemic stroke occurred in 0.5% of patients in the betrixaban group and 0.9% in the enoxaparin group (RR, 0.53; 95% CI, 0.3 to 0.94; P=0.03), ARR = 0.4%, NNT = 250
- Incidence for development of any type of stroke was 0.6% in the betrixaban group and 1.1% in the enoxaparin group (RR, 0.59; 95% CI, 0.35 to 0.97; P=0.03), ARR = 0.5%, NNT = 200
- FDA Black Box Warning: Epidural or spinal hematomas may occur in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture.
Betrixaban – Bevyxxa
• The study was designed to assess the safety and efficacy of extended-duration oral betrixaban compared with standard-duration enoxaparin for thromboprophylaxis in acutely ill medical patients.
• Betrixaban is the first FDA approved anticoagulant indicated for the prevention of VTE in acute medically ill patients both during hospitalization and for an extended period in the ambulatory care environment.
• Betrixaban may also have a role in stroke prevention in patients with atrial fibrillation, in VTE prevention following total hip or knee replacement and treatment of VTE but these are NOT currently FDA approved indications!

Betrixaban – Bevyxxa
• The recommended dose of Betrixaban is an initial single dose of 160 mg, followed by 80 mg once daily. Daily oral doses should be given at the same time of day with food.
  – For patients with severe renal impairment (CrCl ≥ 15 to < 30 mL/min computed by Cockcroft-Gault using actual body weight) or P-gp inhibitors (e.g., amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin) the recommended dose of Betrixaban is an initial single dose of 80 mg followed by 40 mg once daily
• The recommended duration of treatment is 35 to 42 days.
• Available as 40 and 80 mg capsules
• Cost: ~ $485.00/30 x 40 and 80 mg caps
FDA Updates Metformin Dosing Information 4-8-2016

- The labeling recommendations on how and when kidney function is measured in patients receiving metformin will include the following information: before starting metformin, obtain the patient's eGFR.
- Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m².
- Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m² is not recommended.
- Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
- In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m², assess the benefits and risks of continuing treatment. Discontinue metformin if the patient’s eGFR later falls below 30 mL/minute/1.73 m².
- Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m²; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

Empagliflozin – Jardiance New Indication

December 2, 2016

- The U.S. Food and Drug Administration today approved a new indication for Jardiance (empagliflozin) to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease.
- Based on a post market Empa Reg Outcome trial of more than 7,000 patients with type 2 diabetes and cardiovascular disease. In the trial, Jardiance was shown to reduce the risk of cardiovascular death compared to a placebo when added to standard of care therapies for diabetes and atherosclerotic cardiovascular disease.

EMPA-REG OUTCOME Trial

- The primary outcome (CV mortality, non-fatal MI and non-fatal stroke) occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority).
- ARR = 1.6%, NNT 63
- No significant differences in rates of MI or CVA
- No significant difference with 10 vs. 25 mg doses.
- Death from cardiovascular causes (3.7% vs. 5.9% in the placebo group; 38% relative risk reduction; ARR = 2.2%, NNT 46
EMPA-REG OUTCOME Trial

- Hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction)
- Death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction).
- Among patients receiving empagliflozin, there was an increased rate of genital infection (1 in 20 or 5%) but no increase in other adverse events.
  – NEJM on-line 9-17-2015

CVD-REAL Data
American College of Cardiology 66th Annual Scientific Session 19 March 2017

- CV data from a large retrospective international data set including more than 364,000 patients with type-2 diabetes, (87% of whom did not have a history of cardiovascular disease).
  - mean age 57, 44% females
- Treatment with SGLT-2 inhibitors reduced all-cause mortality by 51% and risk of hospitalization for heart failure by 39%.
  - 41.8% of patients were on dapagliflozin, 52.7% on canagliflozin and 5.5% on empagliflozin. (A/Z sponsored the trial)
  - Results are consistent with the Empa-Reg Outcome Trial

EMPA-REG OUTCOME Trial: Renal Data

Microvascular Outcome

- The prespecified composite microvascular outcome in the overall trial population occurred in 577 of 4132 patients (14.0%) in the empagliflozin group and in 424 of 2068 patients (20.5%) in the placebo group, a significant RRR 38% ARR 6.5%, NNT=16
  - the overall result for this composite microvascular outcome was driven entirely by the renal component NEJM on-line June 14, 2016
FDA Drug Safety Update – 6-14-2016

- FDA has strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR).

  - from March 29, 2013, to October 19, 2015, the FDA identified 101 cases of acute kidney injury with sufficient detail to confirm the diagnosis and demonstrate a temporal relationship with canagliflozin (73 patients) and dapagliflozin (28 patients). Hospitalization for evaluation and management of acute kidney injury was necessary in 96 of the 101 cases, 22 were admitted to the ICU. The time to onset of acute kidney injury occurred within one month or less of initiating the drug.

FDA Safety Announcement

- [5-15-2015] The FDA is warning that the SGLT-2 inhibitors: canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization.

- Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness.

SGLT-2 Inhibitors and DKA

- A new analysis from Wake Forest, UNC and Duke) found 39 cases of DKA among 11,197 people with prescriptions for SGLT2 inhibitors (74% in patients with Type 2 DM/ 82% C; 15% D and 3% E). Of these, 26 patients had glucose ≤300 mg/dL, with a mean glucose of 266 mg/dL. Symptoms reported included nausea and vomiting (49%), although researchers said “it is unclear if that was a cause, contributor, or consequence of the DKA.” Also, 67% of the patients had some other obvious event such as surgery, an insulin dose reduction, or weight loss.

- The authors recommend “a high index of suspicion for DKA in patients taking SGLT2 inhibitors with unexplained malaise or gastrointestinal symptoms and recommend measuring urine or plasma ketones in that setting.”

FDA Drug Safety Alert  5-18-2016

• Canagliflozin (Invokana, Invokamet): Drug Safety Communication - Clinical Trial Results Find Increased Risk of Leg and Foot Amputations
  – FDA is alerting the public about interim safety results from an ongoing clinical trial that found an increase in leg and foot amputations, mostly affecting the toes.
  – Patients taking canagliflozin should notify their health care professionals right away if they notice any new pain or tenderness, sores or ulcers, or infections in their legs or feet.

New FDA Safety Alert

• [5-16-2017]: “Based on new data from two large clinical trials, the FDA has concluded that the type 2 diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) causes an increased risk of leg and foot amputations. We are requiring new warnings, including our most prominent Boxed Warning, to be added to the canagliflozin drug labels to describe this risk.”

• Before initiating canagliflozin, consider factors in the patient’s history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.

CANVAS Trial Amputations

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=1,441</th>
<th>Canagliflozin 100 mg N=1,445</th>
<th>Canagliflozin 300 mg N=1,441</th>
<th>Canagliflozin (pooled) N=2,886</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an amputation, n (%)</td>
<td>22 (1.5)</td>
<td>50 (3.5)</td>
<td>41 (3.1)</td>
<td>95 (3.3)</td>
</tr>
<tr>
<td>Total amputations*</td>
<td>35</td>
<td>83</td>
<td>79</td>
<td>162</td>
</tr>
<tr>
<td>Amputation incidence rate (per 1,000 patient-years)</td>
<td>2.8</td>
<td>6.2</td>
<td>5.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>—</td>
<td>2.24 (1.36, 3.69)</td>
<td>2.01 (1.20, 3.34)</td>
<td>2.12 (1.34, 3.38)</td>
</tr>
</tbody>
</table>

* Some patients had more than one amputation

Amputations of the toe and middle of the foot were the most common; however, amputations involving the leg, below and above the knee, also occurred. Some patients had more than one amputation, some involving both limbs.

Canagliflozin combined data 3.3% vs 1.5% placebo; HR 2.12, ARI 1.8%, NNH 56
CANVAS R Trial Amputations

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Canagliflozin 100 mg (with up-titration to 300 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N=2,903</td>
<td>N=2,904</td>
</tr>
<tr>
<td>Patients with an amputation, n (%)</td>
<td>25 (0.9)</td>
<td>45 (1.5)</td>
</tr>
<tr>
<td>Total amputations*</td>
<td>36</td>
<td>59</td>
</tr>
<tr>
<td>Amputation incidence rate (per 1,000 patient-years)</td>
<td>4.2</td>
<td>7.5</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>—</td>
<td>1.80 (1.10, 2.93)</td>
</tr>
</tbody>
</table>

* Some patients had more than one amputation.

Canagliflozin combined data 1.5% vs. 0.9% with placebo; HR 1.90; ARI 0.6%, NNH 167
(This renal safety study was only a mean duration of 2.1 years)

CANVAS and CANVAS R Trials

- Integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk (65.6% had a history of ASCVD). Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks (3.62 years).
- The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
  - Initially tested for non-inferiority (p<0.001) and then if appropriate for superiority (p=0.02)
  - NEJM June 12, 2017 published on-line

CANVAS and CANVAS R Trials

- Primary end-point (CV death, non-fatal MI and non-fatal stroke) 26.9 events/1000 pt years canagliflozin vs. 31.5 placebo; HR = 0.86 (95% CI 0.75-0.97); NNT = ~67
- Secondary end-points (events/1000 patient years)
  - CV death 11.6 vs 12.8; HR = 0.87 (95% CI 0.72-1.06) NS
  - Non-fatal MI 9.7 vs. 11.6; HR = 0.85 (95% CI 0.69-1.05) NS
  - Non-fatal stroke 7.3 vs. 8.4; HR = 0.90 (95% CI 0.71-1.15) NS
  - Hospitalization for heart failure 5.5 vs. 8.7; HR = 0.67 (95% CI 0.52-0.87); NNT = ~89
  - Death any cause 17.3 vs. 19.5; HR = 0.87 (95% CI 0.74-1.01) NS
  - NEJM June 12, 2017 published on-line
CANVAS and CANVAS R Trials

• Progression of albuminuria: 89.4/1000 pt. yrs. Vs. 128.7; HR 0.73 (95% CI 0.67-0.79) NNT = 11
• 40% reduction in eGFR, renal replacement therapy or renal death: 5.5/1000 pt. yrs. Vs. 9.0; HR = 0.60 (95% CI 0.47-0.77); NNT = ~81
  * NEJM June 12, 2017 published on-line

• Diabetic ketoacidosis: 0.6/1000 pt. yrs. vs. 0.3 (p=0.14 NS)
• Amputations: 6.3/1000 pt. yrs. vs. 3.4 (p<0.001) NNH = ~97
• Fractures (all): 15.4/1000 pt. yrs. vs. 11.9 (p=0.02) NNH = ~83
• Volume depletion: 26/1000 pt. yrs. vs. 18.5 (p=0.009) NNH = ~40
• Infection of male genitalia : 34.9/1000 pt. yrs. vs. 10.8 (p<0.001) NNH = ~13
• Female mycotic genital infection: 68.8/1000 pt. yrs. vs. 17.5 (p<0.001) NNH = ~7
  * NEJM June 12, 2017 published on-line

Concerns with SGLT-2 Inhibitors?

• I would not routinely recommend an SGLT-2 inhibitor in the following patients:
  – Patients with impaired renal function (eGFR of < 45 ml/min maybe less than 60?).
  – Patients with diabetic neuropathy, previous foot ulcers, previous amputations and/or peripheral vascular disease.
  – Patients at risk for falls or with orthostatic hypotension.
  – Patients with a history of osteoporosis, osteopenia, decreased BMD or history of fractures.
  – Patients with frequent UTI's or fungal infections
Liraglutide – Victoza
by Novo Nordisk

- A human analog of the glucagon-like peptide-1 (GLP-1) with 97% amino acid sequence homology to endogenous human GLP-1.
  - T1/2 ~11-15 hrs
  - 1.2 mg dose (2 pens/mo)
    - $497.00 GoodRx.com
  - 1.8 mg dose (3 pens/mo)
    - $743.00 GoodRx.com
- Adjunct to diet and exercise for Type 2 DM but not first line and no data in combo with prandial insulin

Liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1–5 studies

Diabetes, Obesity and Metabolism, 11 (Suppl. 3), 2009, 26–34

Liraglutide – Victoza CV Outcomes

- LEADER was a multicenter, international, randomized, double-blind, placebo-controlled trial investigating the long-term effects of liraglutide (1.2 and 1.8 mg) compared to placebo, both in addition to standard of care, in people with type 2 diabetes at high risk of cardiovascular events. The trial was initiated in September 2010 and randomized 9,340 people with type 2 diabetes from 32 countries that were followed for 3.5–5 years. The primary endpoint was the first occurrence of a composite cardiovascular outcome comprising cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.
LEADER CV Safety Trial with Liraglutide

- 9340 patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
- The median follow-up was 3.8 years.
- The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (HR 0.87; 95% CI, 0.78 to 0.97; P<0.001 for noninferiority; P = 0.01 for superiority) ARR 1.9%, NNT=53

LEADER CV Safety Trial with Liraglutide

- Death from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P = 0.007). ARR 1.3%, NNT 77
- The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (HR 0.85; 95% CI, 0.74 to 0.97; P = 0.02). ARR 1.4%, NNT=72

LEADER CV Safety Trial with Liraglutide

- The rates of nonfatal myocardial infarction (HR 0.88), nonfatal stroke (HR 0.89), and hospitalization for heart failure (HR 0.87) were all nonsignificantly lower in the liraglutide group than in the placebo group.
LEADER CV Safety Trial with Liraglutide

- Microvascular Outcomes: The incidence of a composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (HR 0.84; 95% CI, 0.73 to 0.97; P=0.02)
  - The difference was driven by a lower rate of nephropathy events in the liraglutide group (1.5 vs. 1.9 events per 100 patient-years of observation; HR 0.78; 95% CI, 0.67 to 0.92; P=0.003)
  - The incidence of retinopathy events was nonsignificantly higher in the liraglutide group than in the placebo group (0.6 vs. 0.5 events per 100 patient-years; HR 1.15; 95% CI, 0.87 to 1.52; P=0.33).

LEADER CV Safety Trial with Liraglutide

- The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events.
- The incidence of pancreatitis was non-significantly lower in the liraglutide group (18 vs. 23) than in the placebo group.
  - Pancreatic carcinoma 13 (0.3) with liraglutide vs. 5 (0.1) with placebo p=0.06
  - Medullary thyroid carcinoma 0 with liraglutide vs. 1 (<0.1) with placebo p=0.32

Xultophy (IDegLira) by Novo/Nordisk (combination of insulin degludec/Tresiba plus liraglutide/Victoza)

- Liraglutide - Victoza 1.2 mg dose (2 pens/mo) $497.00 GoodRx.com
- 1.8 mg dose (3 pens/mo) $743.00 GoodRx.com
- Insulin Degludec-Tresiba U-100 FlexTouch - 3 mL 100 units/mL - 300 Units/pen – max dose 80 Units in 1 Unit increments – available 5 pens/pack ~$450.00
- The combo price will be about 20% less than the two separately ~ $1,000.00/mo
Insulin degludec plus liraglutide - Xultophy

- **Dosage:** adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily) as an adjunct to diet and exercise.
- The recommended starting dosage is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) QD for all patients
  - Therapy with basal insulin and liraglutide should be discontinued prior to initiation of Xultophy® 100/3.61
  - Dose once daily at the same time each day with or without food
  - If a dose is missed, the patient should resume their once-daily dosing with their next scheduled dose
  - If more than three days have elapsed since the last Xultophy® 100/3.6 dose, reinitiate Xultophy® 100/3.6 at the starting dose (i.e., 16 units) to mitigate any gastrointestinal symptoms

Insulin degludec plus liraglutide - Xultophy

- **Dose Titration:**
  - The label recommends that the patient titrate the dose up or down by 2 units every 3 to 4 days based on self-monitored FPG until the desired FPG is achieved (i.e., 80-130 mg/dL)
  - The maximum daily dosage is 50 units (50 units of insulin degludec and 1.8 mg of liraglutide)
  - If persistent dosages below 16 units or above 50 units are required, discontinue and use alternative therapy (including the two components separately i.e., max dose of liraglutide (1.2 vs. 1.8 mg) plus whatever dose of basal insulin required).
  - Cost: 5 x 3 ml U100/3.6 mg pens $1,020.00

Lixisenatide – Adlyxin by Sanofi

- FDA approved 7-27-2016 a once a day GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
  - Injection: 50 mcg/mL in 3 mL in green prefilled pen (for 14 pre-set doses; 10 mcg per dose)
  - Injection: 100 mcg/mL in 3 mL in burgundy prefilled pen (for 14 pre-set doses; 20 mcg per dose)
  - Cost: ~$600.00/ 2 pens (28 day supply)
  - Initiate at 10 mcg once daily for 14 days. On Day 15, increase dosage to 20 mcg once daily
  - Administer once daily within one hour before the first meal of the day
Lixisenatide – Adlyxin

- You must activate the pen one time before the first use and not again or you will lose doses. The orange window should only appear prior to the first dose which is discarded and thereafter remain white.
- Pull the injection button out firmly until it stops and the arrow will now be pointing towards the needle.
- An insulin needle must be attached to deliver any dose including the discarded initial dose.
- Replace the cap to protect from light.

Lixisenatide vs. Liraglutide

- 26-week, randomized, parallel-group, open-label trial. 404 patients were randomized 1:1 to liraglutide 1.8 mg or lixisenatide 20 µg as add-on to metformin. Liraglutide was administered once daily at any time of the day. Lixisenatide was administered once daily within 1 h prior to the morning or evening meal.
- At week 26, liraglutide reduced HbA1c (primary end point) more than lixisenatide (estimated treatment difference −0.62% [95% CI −0.8; −0.4]; P < 0.0001), with more patients reaching HbA1c <7% and ≤6.5% versus lixisenatide (74.2% and 54.6% for liraglutide vs. 45.5% and 26.2% for lixisenatide; P < 0.0001 for both).
- Both drugs promoted similar body weight decrease (−4.3 kg for liraglutide, −3.7 kg for lixisenatide; P = 0.23).
  — Diabetes Care 2016 Sep; 39(9): 1501-1509.

ELIXA – a cardiovascular safety outcomes trial of lixisenatide

- Lixisenatide (Adlyxin) was FDA approved 7/28/2016
- March 2015, Sanofi announced top-line results of the ELIXA outcome study, a Phase IIIb cardiovascular safety outcomes trial of lixisenatide (Adlyxin®) compared to placebo in 6,000 a high-risk (post ACS) population of adults with Type 2 diabetes for the evaluation of cardiovascular safety.
  - First CV safety trial for any of the GLP-1 Agonists to report out.
- The results from the study showed that lixisenatide was non-inferior, although not superior, to placebo for cardiovascular safety, and establish that there is no additional cardiovascular risk, in a high-risk patient, associated with treatment with lixisenatide, helping to support the existing consensus around the therapeutic benefits of lixisenatide.
  — Results presented at ADA in Boston on June 9, 2015
EXSCEL Trial: Bydureon CV Safety Trial

• EXSCEL is a Phase IIIb/IV, double-blind, placebo-controlled, global CV outcomes trial conducted in 35 countries and enrolled more than 14,000 patients with type-2 diabetes with or without additional CV risk factors or prior CV events. Participants were randomized to receive exenatide once-weekly 2mg or matching placebo by subcutaneous injections. Primary composite CV endpoint risk of MACE, a composite endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke.

  — EXSCEL was run jointly by two academic research organizations - the Duke Clinical Research Institute (Durham, NC, US) and the University of Oxford Diabetes Trials Unit (Oxford, UK)
  — Astra/Zeneca Press Release May 23, 2017

EXSCEL Trial: Bydureon CV Safety Trial

• The EXSCEL trial met its primary safety objective of non-inferiority for MACE. These results address the US Food and Drug Administration (FDA) requirement that medicines to treat T2D are not associated with an increase in CV risk. Fewer CV events were observed in the Bydureon arm of the trial, however, the efficacy objective of a superior reduction in MACE did not reach statistical significance.

  — A full evaluation of the EXSCEL data is ongoing. The results will be presented at the European Association for the Study of Diabetes (EASD) annual meeting on Thursday, 14 September 2017 in Lisbon, Portugal.
Bydureon Pen – Extended Release Exenatide

- 2 mg pens: remove from refrigerator 15 min prior to reconstituting.
- Attach needle to the pen
- Hold the pen straight up and turn the knob until the green part of the pen disappears and it clicks, then tap the pen in the palm of you hand to mix the medication, turning the pen every 10 taps (up to 80 times or more) and check for even mixing
- Still holding the pen upright, you must now expel any air in the pen by pushing the knob until the orange part of the pen disappears and the injection button is released.
- Pull off the needle cover and inject.
  - Cost $670.00 for 4 pens

Soliqua™ 100/33 (insulin glargine & lixisenatide injection) 100 Units/mL & 33 mcg/mL

- Soliqua 100/33 will be delivered in a single pre-filled pen for once-daily dosing covering 15 to 60 Units of insulin glargine 100 Units/mL and 5 to 20 mcg of lixisenatide using SoloStar technology, Soliqua 100/33 will be available in U.S. retail pharmacies in January 2017.
  - Price ~$680.00/5 pens GoodRx.com 1-25-2017

Soliqua™ 100/33 (insulin glargine & lixisenatide injection) 100 Units/mL & 33 mcg/mL

Dosage and Administration:
- Discontinue therapy with lixisenatide or basal insulin prior to initiation of Soliqua 100/33.
- In patients inadequately controlled on less than 30 units of basal insulin or on lixisenatide, the starting dosage is 15 units (15 units insulin glargine/5 mcg lixisenatide) given subcutaneously once daily.
- In patients inadequately controlled on 30 to 60 units of basal insulin, the starting dosage is 30 units (30 units insulin glargine/10 mcg lixisenatide) given subcutaneously once daily.
- Inject once a day within the hour prior to the first meal of the day.
  - Maximum daily dosage is 60 units (60 units of insulin glargine and 20 mcg of lixisenatide).
  - Soliqua 100/33 Pen delivers doses from 15 to 60 units with each injection.
Insulin Glargine – Basaglar by Lilly and BI

- Dec 16, 2015 FDA approved Basaglar (insulin glargine) but not launched until after Dec 2016 based upon court action. The first insulin product approved through an abbreviated approval pathway under the FDA 505(b)(2) application which did rely partly on the safety and effectiveness of Lantus (insulin glargine by Sanofi).
- Lilly just announced the price will be ~15% lower than Lantus
- Cost: ~$343.00 per box of 5 pens vs. Lantus $403.00 per box of 5 pens

The FDA determined that Basaglar was sufficiently similar to Lantus and in addition Basaglar was studied in two large trials (543 Type 1 and 744 Type 2 patients with diabetes), like Lantus FDA approved for patients age 6 and up.

Basaglar is considered a “follow-on” NOT FDA approved as a “Biosimilar” product. (There is no reference listed drug for Lantus under the Public Health Services Act)

Insulin Glargine U100 – MK1293 by Merck/Samsung Bioepis

- Merck has also filed for FDA approval 8/2016 for U 100 insulin glargine known as MK1293. In two phase 3 trials MK-1293 achieved its primary endpoint by demonstrating non-inferiority in change from baseline A1C and similar safety to Lantus® (insulin glargine) after 24 weeks in patients with type 1 and type 2 diabetes.
- As with Lilly’s Basaglar, Sanofi is expected to also file a patent infringement suit against Merck and Samsung if their biosimilar nears registration, prompting an immediate 30-month injunction on launch.

Insulin Glargine U100 by Mylan/Biocon

- Mylan and Biocon Ltd (India’s largest biopharmaceutical Co.) announced that the European Medicines Agency (EMA) in Nov 2016 has accepted for review Mylan’s Marketing Authorization Application (MAA) for insulin glargine, a long-acting insulin analog used to treat adults with type 2 diabetes and adults and pediatric patients (children 6 years and older) with type 1 diabetes for the control of high blood sugar.
  - Biocon and Mylan are exclusive partners on a broad portfolio of biosimilars and insulin analogs. Glargine is one of the three insulin analogs (lispro and aspart) being co-developed by Mylan and Biocon for the global marketplace. Mylan has exclusive commercialization rights for insulin glargine in the U.S., Canada, Australia, New Zealand, the European Union and European Free Trade Association countries.
  - Biocon has exclusive rights for Japan and a few emerging markets; and co-exclusive commercialization rights with Mylan in the rest of the world.
DEVOTE Trial

- DEVOTE (Cardiovascular Safety of Insulin Degludec vs. Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events)
- Patients were randomized in a double-blind fashion to receive either insulin degludec (n=3818) or glargine (n=3819).
- Primary composite outcome was first occurrence of 3-point MACE (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke).
- Secondary endpoints included severe hypoglycemia (defined as an episode requiring assistance from another person or an episode temporally associated with an accident, convulsion, or death) and change from baseline in HbA1c, fasting plasma glucose, and total insulin dose by trial end.

- NEJM June 12, 2017 published on-line

DEVOTE Trial

- The primary outcome occurred in 325 patients (8.5%) in the degludec group and in 356 (9.3%) in the glargine group (hazard ratio, 0.91; 95% CI 0.78 to 1.06; P<0.001 for noninferiority).
- At 24 months, the mean glycated hemoglobin level was 7.5±1.2% in each group, whereas the mean fasting plasma glucose level was significantly lower in the degludec group than in the glargine group (128±56 vs. 136±57 mg per deciliter, P<0.001).
- Prespecified adjudicated severe hypoglycemia occurred in 187 patients (4.9%) in the degludec group and in 252 (6.6%) in the glargine group, ARR = 1.7% (rate ratio, 0.60; P<0.001 for superiority; odds ratio, 0.73; P<0.001 for superiority). NNT = 59
- Rates of adverse events did not differ between the two groups.

- NEJM June 12, 2017 published on-line

New Ultra-Rapid Insulin Aspart – Fiasp

by Novo-Nordisk

- Sept. 29, 2017 the U.S. Food and Drug Administration (FDA) approved Fiasp® (insulin aspart injection) 100 Units/mL, a fast-acting mealtime insulin indicated to improve glycemic control in adults with type 1 and type 2 diabetes.
- Fiasp® can be dosed at the beginning of a meal or within 20 minutes after starting a meal. Fiasp® is a new formulation of NovoLog®, in which the addition of niacinamide (vitamin B3) helps to increase the speed of the initial insulin absorption, resulting in an onset of appearance in the blood in approximately 2.5 minutes.
- Fiasp® will be available in a pre-filled delivery device FlexTouch® pen and a 10 mL vial at the same price as Novolog
New Ultra-Rapid Insulin Aspart – Fiasp

- Pharmacokinetic results from a euglycemic clamp study in adult patients with type 1 diabetes (N=51) showed that insulin aspart appeared in the circulation ~ 2.5 minutes and maximum insulin concentrations was achieved ~63 minutes after administration of FIASP. T1/2 elimination is ~1.1 hrs.
- If converting from another mealtime insulin to FIASP, the change can be done on a unit-to-unit basis.
- DO NOT dilute or mix FIASP with any other insulin products or solutions, except infusion fluids.
- May be stored at room temperature for up to 28 days.

Label Change for Inhaled Insulin Afrezza

October 2, 2017

<table>
<thead>
<tr>
<th>Parameter for Insulin Effect of Available Cartridge Forms</th>
<th>AFREZZA 4 units</th>
<th>AFREZZA 12 units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first measurable effect</td>
<td>~12 minutes</td>
<td>~12 minutes</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>~35 minutes</td>
<td>~45 minutes</td>
</tr>
<tr>
<td>Time for effect to return to baseline</td>
<td>~90 minutes</td>
<td>~180 minutes</td>
</tr>
</tbody>
</table>

Mealtime AFREZZA Starting Dose Conversion Table (Dose is administered at the beginning of the meal)

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 ≥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 ≥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 ≤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 ≥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%


Long-term Aspirin Prevention of CVD and Cancer

- A significant reduction of 22 percent in non-fatal MI over 10 years.
- No significant reduction on nonfatal stroke (combining ischemic stroke, for which a benefit is postulated and hemorrhagic stroke, for which a risk is postulated) over 10 years.
- A significant reduction of 24 percent in colon cancer incidence over long-term follow-up (20 years).
- A significant reduction of 35 percent in colorectal cancer mortality over long-term follow-up (20 years).
- A possible reduction of 6 to 8 percent in overall mortality over 10 years.
  - UpToDate accessed 4-21-2017

<table>
<thead>
<tr>
<th>Indication</th>
<th># Trials</th>
<th>Antiplatelet %</th>
<th>Control %</th>
<th>O.R./ARR/NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>12</td>
<td>13.5%</td>
<td>17.0%</td>
<td>25%/2.5%/29</td>
</tr>
<tr>
<td>Acute MI</td>
<td>15</td>
<td>10.4%</td>
<td>14.1%</td>
<td>30%/2.8%/27</td>
</tr>
<tr>
<td>Prior CVA/TIA</td>
<td>21</td>
<td>17.8%</td>
<td>21.4%</td>
<td>22%/3.6%/28</td>
</tr>
<tr>
<td>Acute Stroke</td>
<td>7</td>
<td>8.2%</td>
<td>9.1%</td>
<td>11%/0.9%/111</td>
</tr>
<tr>
<td>Other High Risk</td>
<td>140</td>
<td>8.0%</td>
<td>10.2%</td>
<td>28%/2.2%/46</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>12</td>
<td>8.0%</td>
<td>13.3%</td>
<td>46%/3.3%/19</td>
</tr>
<tr>
<td>Stable Angina (CHD)</td>
<td>7</td>
<td>9.9%</td>
<td>14.1%</td>
<td>13%/4.2%/24</td>
</tr>
<tr>
<td>Peripheral Arterial DIs</td>
<td>42</td>
<td>5.8%</td>
<td>7.1%</td>
<td>23%/1.3%/77</td>
</tr>
<tr>
<td>All Trials</td>
<td>195</td>
<td>10.7%</td>
<td>12.2%</td>
<td>22%/3.0%/40</td>
</tr>
<tr>
<td>Primary Prevention</td>
<td>3</td>
<td>4.5%</td>
<td>4.9%</td>
<td>10%/0.4%/250</td>
</tr>
</tbody>
</table>

Secondary Prevention: Effect of antiplatelet therapy on vascular events (nonfatal MI, nonfatal stroke, and vascular death)

*There was no difference in efficacy between doses of 75 to 150 mg/day (called low-dose aspirin) and 160 to 325 mg/day (medium dose aspirin)

Modified from 2012 UpToDate®
Aspirin Formulation?

- **ENTERIC-COATED AND BUFFERED ASPIRIN** — It has been proposed that a way to prevent gastrointestinal toxicity from aspirin is the use of enteric-coated or buffered aspirin. Enteric-coated aspirin is designed to resist disintegration in the stomach, dissolving in the more neutral-to-alkaline environment of the duodenum.
- Although enteric-coated aspirin diminishes endoscopic signs of gastro-duodenal injury, it does not appear to protect against the clinically relevant end point of gastrointestinal bleeding. Bleeding is thought to reflect the systemic rather than the topical effects of aspirin and probably explains why buffered aspirin is no more effective than plain aspirin in preventing ulcer bleeding.
- **Bottom Line:** No benefit in reducing GI risk.

Which Aspirin Formulation?

- In some, but not all studies, equivalent doses of enteric coated aspirin are not as effective as plain aspirin. Lower bio-availability of these preparations and poor absorption from the higher pH environment of the small intestine may result in inadequate platelet inhibition, particularly in heavier subjects. These data contribute to the formulation of the hypothesis that low dose enteric coated aspirin does not produce adequate platelet inhibition.
- In acute occlusive vascular events (e.g., acute coronary syndrome), the necessity to achieve a rapid clinical antithrombotic effect precludes the recommendation of enteric coated aspirin because of its delayed absorption. If the only available preparation is enteric coated, the single tablet or multiple tablets necessary to achieve the recommended dose of 325mg should be crushed or chewed.

Dose of Aspirin?

- At present, the United States Food and Drug Administration recommends daily doses of 75 to 325 mg, while the 2006 American College of Cardiology /American Heart Association (ACC/AHA) guidelines on secondary prevention recommends daily doses of 75 to 162 mg for secondary prevention. The ACCP recommends a daily dose of 75 to 100 mg (i.e. 81 mg)
- In patients with acute occlusive events, a loading dose of at least 162 mg aspirin and preferably 325 mg should be given to achieve a rapid clinical antithrombotic effect.
House Dust Mite Allergen Extract – Odactra
by Merck

- March 1, 2017 the FDA approved Odactra, the first allergen extract to be administered under the tongue (sublingually) to treat house dust mite (HDM)-induced nasal inflammation (allergic rhinitis), with or without eye inflammation (conjunctivitis), in people 18 through 65 years of age. one of the most common causes of perennial allergies.
- House dust mite allergies are a reaction to tiny bugs (Dermatophagoides farinae and Dermatophagoides pteronyssinus) that are commonly found in house dust. Dust mites, close relatives of ticks and spiders, are too small to be seen without a microscope. They are found in bedding, upholstered furniture and carpeting. Individuals with house dust mite allergies may experience a cough, runny nose, nasal itching, nasal congestion, sneezing, and itchy and watery eyes.

House Dust Mite Allergen Extract – Odactra

- Odactra is indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by in vitro testing for IgE antibodies to Dermatophagoides farinae (Der far) or Dermatophagoides pteronyssinus (Der pte) house dust mites, or skin testing to licensed house dust mite allergen extracts.
- It is a freeze dried allergen extract of HDM allergen extracts of Der far and Der pte in a tablet for sublingual allergen immunotherapy (SLIT). The dosage is only available as 12 SQ-HDM tablets. SQ is a method of standardization of biological potency, major allergen content and complexity of the allergen extract.

FDA approval was based on 3 pivotal trials:
- An environmental exposure chamber (EEC) trial done in a single center in Austria
  - 124 adult subjects 18 years of age and older with HDM-induced rhinitis with or without conjunctivitis with or without asthma were randomized 1:1:1 to receive either placebo (n=41), Odactra 6 SQ-HDM (n=41), or Odactra 12 SQ-HDM (n=42). Subjects received daily dosing with Odactra or placebo for 24 weeks prior to a 6 hour challenge in an EEC with a continuous high concentration of HDM allergen (approximately 0.3 grams HDM allergen mixture containing 10:10:1 Der far whole bodies, Der pte whole bodies, and feces from both species), which reflects the composition of mite material during natural exposure. Prior to the challenge sessions, subjects were required to stop their medications to treat allergic rhinitis and conjunctivitis symptoms but were allowed to use rescue medications while in the EEC.
House Dust Mite Allergen Extract – Odactra

- While in the EEC, subjects recorded the presence of nasal symptoms (itchy nose, blocked nose, runny nose, and sneezing) every 15 minutes in electronic diaries. Scores were assigned for each symptom based on a 4-point rating scale (0=none to 3=severe) and summed in order to calculate the total nasal symptom score (TNSS). The primary efficacy endpoint was to evaluate the difference in the average TNSS between treatment and placebo group during the chamber session at Week 24. No pre-specified criteria for success were defined. **The treatment difference between Odactra 12 SQ-HDM and placebo was -48.6% (95% CI: -60.2%, -35.3%).**

House Dust Mite Allergen Extract – Odactra

North American Field Efficacy Study;

- A Phase 3 double-blind, randomized, placebo-controlled field efficacy study was conducted in the U.S. and Canada, enrolling 1482 adolescent and adult subjects 12 years of age and older with HDM-induced allergic rhinitis with (48%) or without conjunctivitis, with (31%) or without asthma. Patients were randomized 1:1 to receive either Odactra 12 SQ-HDM(n=741) or placebo (n=741) once daily for 52 weeks.

- The efficacy was assessed through self-reporting of symptoms and medication use. Based on these self-assessments, the Total Combined Rhinitis Score (TCRS), daily symptom scores (DSS) and daily medication scores (DMS) for rhinoconjunctivitis were calculated.

House Dust Mite Allergen Extract – Odactra

- Daily symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) and two ocular symptoms (gritty/itchy eyes and watery eyes). Each of these rhinoconjunctivitis symptoms was individually graded by subjects daily on a scale of 0 (none) to 3 (severe) and then summed. Subjects in active and placebo arms of this study were allowed to take symptom-relieving allergy medications (including oral and ocular antihistamines and nasal corticosteroids) during the study as needed. The DMS measured the use of these standard symptom-relieving allergy medications. Predefined daily maximum scores were assigned to each class of rhinitis and conjunctivitis medication as 0=none, 6=oral antihistamine, 6=ocular antihistamine, and 8=nasal corticosteroid.
House Dust Mite Allergen Extract – Odactra

• The primary endpoint was the difference between the treatment and placebo groups in the average TCRS during approximately the last 8 weeks of treatment. The TCRS represents the sum of the daily rhinitis DSS and the rhinitis DMS. Subjects in this study were required to stop taking symptom-relieving allergy medication during the baseline period. The mean rhinitis DSS at baseline was 7.94 out of 12 total points in both the treatment arm and in the placebo arm.

House Dust Mite Allergen Extract – Odactra

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ODACTRA Score</th>
<th>Placebo Score</th>
<th>Treatment Difference (ODACTRA-Placebo)</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>4.10</td>
<td>4.95</td>
<td>-0.80</td>
<td>-17.2% (-26.0%, -9.7%)</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis DSS</td>
<td>3.55</td>
<td>4.20</td>
<td>-0.65</td>
<td>-15.5% (-24.4%, -7.3%)</td>
</tr>
<tr>
<td>Rhinitis DMS</td>
<td>0.65</td>
<td>0.79</td>
<td>-0.15</td>
<td>-16.4% (-4.1%, 4.3%)</td>
</tr>
<tr>
<td>TCS</td>
<td>5.56</td>
<td>6.60</td>
<td>-1.10</td>
<td>-16.7% (-24.6%, -8.0%)</td>
</tr>
</tbody>
</table>

**Note:** Efficacy less than with SCIT and most patients will probably still need symptomatic treatments with antihistamines and/or nasal steroids but it may be slightly more effective than montelukast, antihistamines and nasal steroids (UpToDate accessed 4-21-2017)

House Dust Mite Allergen Extract – Odactra

– The number of patients less than 18 years of age was limited as there were only 189 12-17 y/o patients in the NA Field Study.

– European Field Efficacy Study in 992 adults produced similar results.

– CONTRAINDICATIONS:
  – Severe, unstable or uncontrolled asthma
  – History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy
  – A history of eosinophilic esophagitis
The timing of the adverse reaction relative to exposure to Odactra was evaluated for 7 solicited adverse reactions (itching in the ear, itching in the mouth, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat irritation/tickle, and throat swelling). The median time to onset of these adverse reactions following initiation of treatment with Odactra varied from 1 to 7 days. The median duration of these adverse reactions that occurred on the first day of treatment initiation varied from 30 to 60 minutes. These adverse reactions recurred for a median of 2 to 12 days.

House Dust Mite Allergen Extract – Odactra

**WARNING: SEVERE ALLERGIC REACTIONS**

- ODACTRA can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)
- Do not administer ODACTRA to patients with severe, unstable or uncontrolled asthma. (4)
- Observe patients in the office for at least 30 minutes following the initial dose. (5.1)
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)
- ODACTRA may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)
- ODACTRA may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)

House Dust Mite Allergen Extract – Odactra

- Administer the first dose in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. After receiving the first dose of Odactra, observe the patient for at least 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the patient tolerates the first dose, the patient may take subsequent doses at home.
- The patient should administer Odactra as follows:
  - Take the tablet from the blister unit after carefully removing the foil with dry hands. Place the tablet immediately under the tongue where it will dissolve within 10 seconds.
  - Do not swallow for at least 1 minute.
  - Wash hands after handling the tablet.
  - Do not take the tablet with food or beverage.
  - Food or beverage should not be taken for 5 minutes after taking the tablet.
  - Data regarding the safety of restarting treatment after missing a dose are limited. In the clinical studies, treatment interruptions for up to seven days were allowed.
  - Prescribe auto-injectable epinephrine to patients prescribed Odactra and instruct patients in the proper use.
House Dust Mite Allergen Extract – Odactra

• Cost: ??? But Ragwitek and Grastek sublingual tabs for ragweed and grass pollen are both about $300.00/month

• What is the minimal amount of time required to see a clinical effect? (UpToDate accessed 4-21-2017)
  – The minimal amount of time required to see a clinical effect with SLIT may vary somewhat depending upon the allergen (seasonal versus perennial). Clinical trials of grass or ragweed tablets have shown that treatment effect is optimized with initiation of treatment 12 to 16 weeks prior to the onset of pollen season. In contrast, an environmental chamber study design with house dust mite SLIT demonstrated an early onset of action at eight weeks, whereas a natural field trial showed an onset of action at four months.

House Dust Mite Allergen Extract – Odactra

• How effective is SLIT for the polysensitized patient?
  – The most compelling data for use of SLIT is in the monosensitized pediatric or adult patient with seasonal allergic rhinoconjunctivitis, with or without mild asthma. Nearly all of the high quality studies available have shown benefit in this context. However, the typical patient in North America is sensitized to multiple aeroallergens, both seasonally and perennially. At present, the few multiple allergen studies performed in the United States have not shown clinical benefit. (UpToDate 4-2017)