

New Drug Update 2018-19

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Faculty Disclosure

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

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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.”**

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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

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HPV-9 Vaccine

- **What is the recommendation for persons with immunocompromising conditions?**
- **CDC recommends 3 doses of HPV vaccine (0, 1–2, 6 months) for immunocompromised people age 9 through 26 years.**
- **People whose immune responses might be lower, for example due to HIV infection, cancer, autoimmune disease, or taking immunosuppressant medications, should receive 3 doses to make sure they get the most benefit.**
- **However, children with asthma, diabetes, and other conditions that would not suppress immune response to HPV vaccination can receive a 2-dose schedule.**

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HPV-9 Vaccine

- **October 5, 2018 the FDA approved Human Papillomavirus (HPV) 9-valent Vaccine, Recombinant (Gardasil-9) expanding the approved use of the vaccine to include women and men aged 27 through 45 years of age.**
- **In approximately 3,200 women 27 through 45 years of age, followed for an average of 3.5 years, HPV-9 vaccine (Gardasil-9) was 88 percent effective in the prevention of a combined endpoint of persistent infection, genital warts, vulvar and vaginal precancerous lesions, cervical precancerous lesions, and cervical cancer related to HPV types covered by the vaccine.**
- **Data in men is based upon immunogenicity data from a clinical trial in which 150 men, 27 through 45 years of age, received a 3-dose regimen of HPV-9 vaccine (Gardasil-9) over 6 months.**
- **The ACIP reviewed the data on October 25, 2018 and voted during meeting on June 26, 2019.**

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ACIP Meeting 6-26-2019

- In a **10-4 vote**, the committee also recommended adults ages 27 through 45 who had not been adequately vaccinated make shared decisions with their doctors about getting vaccinated with the HPV-9 vaccine. Adults older than 45 who had not been vaccinated are not advised to do so, since HPV vaccines are not licensed for use in that age group.
- **Consider patients with new or multiple sexual partners or other high-risk patients who have not been vaccinated previously?**
 - MMWR August 16, 2019 / 68(32);698–702

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PCV-13 Vaccine for patients 65 and older?

- 6-26-2019 the **ACIP vote** was close, with eight members voting to remove the recommendation of PCV-13 vaccine for all patients age 65 and older and six voting to continue it. In a 13-1 vote that followed, the committee recommended what's known as a "shared clinical decision making" — in effect leaving it up to doctors and their patients aged 65 and older to decide whether they should get a single dose of Prevnar 13.
- In 2014 the committee agreed that it might need to revisit the advice because of the effect the vaccine was having in children, who also receive it. In short, **older adults were benefiting from the use of the vaccine in small children. With fewer kids sick with pneumococcus, fewer cases in older adults were being seen as well.**

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Who might benefit the most from PCV-13?

- In a review of medical data from a community in Finland the following conditions were significantly more common among pneumonia patients than among control subjects: **heart disease (38.4% versus 23.0%), lung disease (13.0% versus 3.8%), bronchial asthma (11.9% versus 3.1%), immunosuppressive therapy (2.7% versus 0.8%), alcoholism (2.2% versus 0.3%), and institutionalization (8.6% versus 3.9%).** (The American Journal of Medicine 1994; 96:313-320)

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Tdap (Adacel Vaccine) by Sanofi Pasteur

- **January 15, 2019 - The Food and Drug Administration (FDA) has expanded the use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis [Tdap] vaccine adsorbed (Adacel, Sanofi Pasteur) to allow for repeat vaccination in patients 10–64 years old \geq 8 years after the first Tdap vaccination.** Adacel is approved for active booster immunization against tetanus, diphtheria, and pertussis.
- The approval was **based on data from the Td537 study** which included individuals 18–64 years old who had received a dose of Adacel 8–12 years prior (N=1330). **Participants were randomized to receive either a second dose of Adacel (N=1002) or Td vaccine (tetanus and diphtheria toxoids adsorbed; N=328).** Blood samples for immunogenicity analyses were obtained from participants pre-vaccination and approximately 28 days post-vaccination, the **rates of seroprotection against tetanus and diphtheria were >99% in both groups.**

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Hepatitis A Update 2018

- **ACIP Meeting Oct 2018: Hepatitis A vaccination: Homelessness**

- ACIP Working Group Recommendations:

- **Pros:** Protection of a vulnerable population
- Providers are more likely to administer vaccine to homeless persons if homelessness is an ACIP recommended indication for vaccination
- Vaccination of homeless persons would reduce an at risk population and therefore reduce the risk of large-scale outbreak, and increase the herd immunity among the homeless population over time
- Vaccinating homeless in an outbreak setting and controlling an outbreak among homeless is challenging compared to integrating services into a familiar setting
- Routine vaccination is likely less costly than vaccination as part of an outbreak response
- **Cons:** Vaccine administration record-keeping
- Limited published data exist on hepatitis A or vaccination that specifically focuses on persons who are homeless
- Routine vaccination of homeless who do not utilize health services might not be feasible

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FDA Head Warns Feds May Intervene if States Don't Strengthen Vaccine Laws

- 2-20-2019 FDA commissioner Scott Gottlieb said that the **federal government may have to take action if states don't strengthen their laws on vaccine exemptions**, CNN reports.
- **Seventeen states allow families to choose not to vaccinate their children based on personal beliefs. Forty-seven states allow religious exemptions.**
- **Measles outbreaks in the U.S. have infected 127 people so far in 2019; most were unvaccinated. (4/3/2019 465 cases including 150+ from Rockland County, NY)**

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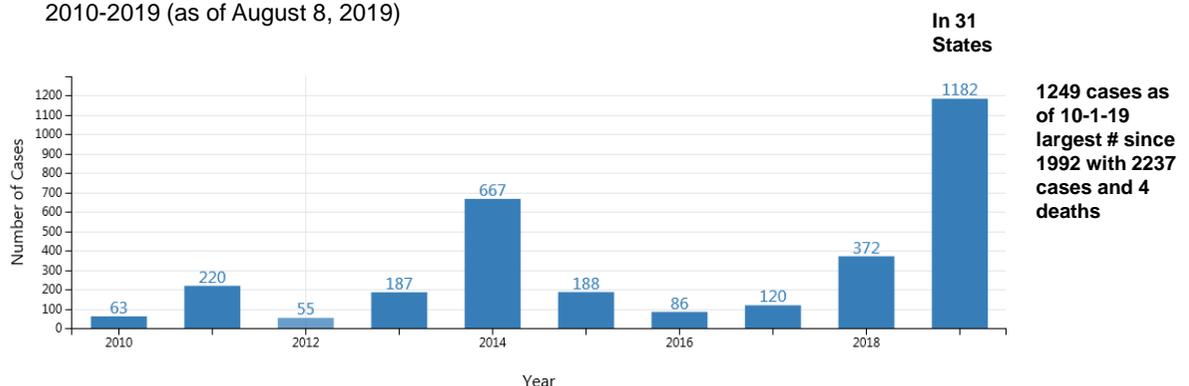
'Unethical Physicians' Aid Surge in Vax Exemptions

- At two public charter schools in the Sonoma wine country town of Sebastopol, more than half of the kindergartners received medical exemptions from state-required vaccines last school year. The cities of Berkeley, Santa Cruz, Nevada City, Arcata, and Sausalito all had schools in which more than 30% of the kindergartners had been granted such medical exemptions. (CDC estimates medical exemptions should be a fraction of 1% and include children who are allergic to vaccine components, who have had a previous reaction to a vaccine, or whose immune systems are compromised, including kids being treated for cancer).
- Nearly three years ago, with infectious disease rates ticking up, California enacted a fiercely contested law barring parents from citing personal or religious beliefs to avoid vaccinating their children. Children could be exempted only on medical grounds, if the shots were harmful to health. (Miss, WV and now Maine have passed similar legislation while Washington has just eliminated the personal exemption)
- Some physicians are wielding that power liberally and sometimes for cash: signing dozens -- even hundreds -- of exemptions for children in far-off communities. (MedPage Today 4-10-2019)

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US Measles Cases and Outbreaks

Number of Measles Cases Reported by Year
2010-2019 (as of August 8, 2019)



As of August 8, 2019, 124 of the people who got measles this year were hospitalized, and 64 reported having complications, including pneumonia and encephalitis.

<https://www.cdc.gov/measles/cases-outbreaks.html>

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Measles

- **In 2000, endemic measles was declared “eliminated” from the U.S.** (absence of continuous disease transmission for greater than 12 months)
- **Importation of measles will continue to occur as measles is endemic in many other parts of the world.**
- Measles cases are still reported in the U.S., including among adults - **Most cases related to travelers who bring measles back from overseas (2/3 from unvaccinated U.S. residents, 1/3 from unvaccinated foreign visitors)**
- **2 doses of MMR (measles-mumps-rubella) vaccine are 97% effective at preventing measles; 1 dose is 93% effective. Protection lasts for life.**
- The majority of people who get measles are unvaccinated.
 - <http://www.immunize.org/cdc/cdc-measles-us-3-28-2019.pdf>

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Mumps Outbreak

- **Update: Mumps Outbreak at Temple University in Philadelphia March 25, 2019**
 - Following a large second wave of transmission, the **number of mumps cases associated with the Temple University outbreak has increased to 99.**
- **From January 1 to July 19, 2019, 45 states and the District of Columbia in the U.S. reported mumps infections in 1,799 people to CDC.**
- **Recognition, Testing, and Management:**
 - When evaluating patients with parotitis without an apparent cause, area providers should recognize the increased likelihood of mumps infection among patients who are associated with Temple University and **consider mumps infection in other patients with parotitis.**

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Baloxavir marboxil (Xofluza) by Shionogi/Roche

- **Oct 24, 2018** the FDA approved baloxavir marboxil (Xofluza) for the **treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours**. The drug is the first new medication for influenza with a novel mechanism in the last 20 years and it was **granted Priority Review by the FDA**.
- A **single-dose oral medicine** with a novel proposed mechanism of action that **inhibits polymerase acidic endonuclease, an enzyme essential for viral replication** with **demonstrated efficacy against a wide range of influenza viruses, including oseltamivir-resistant strains and avian strains (H7N9, H5N1)** in non-clinical studies.
- In clinical trials of baloxavir marboxil, **resistant viruses were detected in 23.4 percent of participating patients younger than 12 years old in Japan**.

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Baloxavir marboxil (Xofluza)

- **CAPSTONE-1** was a phase III multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of Xofluza in 1,436 people age 12 and older in the US and Japan during the 2016-2017 season.
- The primary endpoint of the study was time to alleviation of symptoms.
- Doses: **weight-based single doses of baloxavir (40-79 Kg = 40 mg and \geq 80 Kg = 80 mg) and oseltamivir 75 mg twice daily for 5 days. (Available as 2 or 4 x 20 mg tabs and 1 or 2 x 40 mg tabs per blister card)**
~\$165.00/single dose GoodRx.com 11-26-18
- **Oseltamivir (Tamiflu) 75 mg x 10 caps Brand ~\$165.00 and generic ~\$50.00 GoodRx.com 11-26-18**
– N Engl J Med 2018; 379:913-923

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Baloxavir marboxil - Xofluza

- The **median time to alleviation of influenza symptoms was 23.4 to 28.2 hours shorter in the baloxavir groups than in the placebo group (P<0.05)**. In the phase 3 trial, the intention-to-treat infected population included 1064 patients; **84.8 to 88.1% of patients in each group had influenza A(H3N2) infection. The median time to alleviation of symptoms was 53.7 hours (95% confidence interval [CI], 49.5 to 58.5) with baloxavir, as compared with 80.2 hours (95% CI, 72.6 to 87.1) with placebo (P<0.001)**. The **time to alleviation of symptoms was similar with baloxavir and oseltamivir (median time 54 hours versus 54 hours)**. Baloxavir was associated with greater reductions in viral load 1 day after initiation of the regimen than placebo or oseltamivir. (N Engl J Med 2018; 379:913-923)
- Adverse events were reported in 20.7% of baloxavir recipients, 24.6% of placebo recipients, and 24.8% of oseltamivir recipients.

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Baloxavir marboxil (Xofluza)

- Roche recently announced that the **global phase III CAPSTONE-2** study assessing the safety and efficacy of baloxavir marboxil in people at high risk of complications from the flu, as defined by the CDC, met the study's primary objective and showed superior efficacy in the primary endpoint of time to improvement of influenza symptoms versus placebo.
 - Result: Among **2184 randomized pts**, 1163(53%) comprised the ITTI population (**47.9% A/H3N2, 6.9% A/H1N1, 41.6% B**). The most common risk factors were **asthma or chronic lung disease(39.2%) and age ≥65 years (27.4%)**. **Time to improvement in flu symptoms (TTIIS) was significantly shorter in BXM than PLC (median 73.2hr vs 102.3hr, p<0.0001) and numerically shorter than Os (81.0 hr, p=0.8347)**. TTIIS in BXM pts with A/H3N2 virus (median: 75.4 hr) was significantly shorter than in PLC (100.4 hr; P =0.0141) and was significantly shorter in pts with influenza B (74.6 hr) than in either PLC (100.6 hr; P =0.0138) or Os (101.6 hr; P =0.0251). (ID Week 2018 Late Breaker-Saturday, October 6, 2018: 10:50 AM)

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Baloxavir marboxil (Xofluza)

- $T_{1/2}$ ~ 79 hours
- Weight based dose taken with or without food
- **Co-administration of baloxavir with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) reduce plasma concentrations and should be avoided.**
- LAIV should not be considered effective if treated with baloxavir if administered concurrently or within about 2 weeks after LAIV

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

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C on average, by approximately $\geq 50\%$ ^a	Daily dose lowers LDL-C on average, by approximately 30% to $< 50\%$	Daily dose lowers LDL-C on average, by $< 30\%$
Atorvastatin (40⁺)–80 mg Rosuvastatin 20 (40) mg	Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg[‡] Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid <i>Pitavastatin 2–4 mg</i>	<i>Simvastatin 10 mg</i> Pravastatin 10–20 mg Lovastatin 20 mg <i>Fluvastatin 20–40 mg</i> <i>Pitavastatin 1 mg</i>
Specific statins and doses are noted	in bold that were evaluated in RCTs.	

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Top 10 Top 10 Take Home Messages

3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.

- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥ 70 mg/dL (≥ 1.8 mmol/L). (NNT at 7 years 50 IMPROVE-IT Trial)
- In patients at very high risk whose LDL-C level remains ≥ 70 mg/dL (≥ 1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, (NNT 30 at 2.8 years LDL ≥ 100 mg/dl Odyssey Outcomes Trial, NNT 50 at 3 years Fourier Trial) although the long-term safety (>3 years) is uncertain



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Top 10 Top 10 Take Home Messages

4. In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL [≥ 4.9 mmol/L]) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

- If the LDL-C level remains ≥ 100 mg/dL (≥ 2.6 mmol/L), adding ezetimibe is reasonable
- If the LDL-C level on statin plus ezetimibe remains ≥ 100 mg/dL (≥ 2.6 mmol/L) & the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety (>3 years) is uncertain and economic value is low at mid-2018 list prices.



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IMPROVE-IT: Results

- 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.
 - N Engl J Med 2015;372:2387-97

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IMPROVE-IT

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

Clinical Outcomes	Simvastatin, n=9077 (%)	Ezetimibe/Simvastatin, n=9067 (%)	P
Primary end point (Cardiovascular death, MI, unstable angina, coronary revascularization, or stroke)	34.7	32.7	0.016
All-cause death	15.3	15.4	0.782
MI	14.8	13.1	0.002
Stroke	4.8	4.2	0.052
Ischemic stroke	4.1	3.4	0.008
Unstable angina	1.9	2.1	0.618
Coronary revascularization	23.4	21.8	0.107

Primary combined endpoint at 7 years: RRR 6.4%; ARR 2.0%; NNT 50

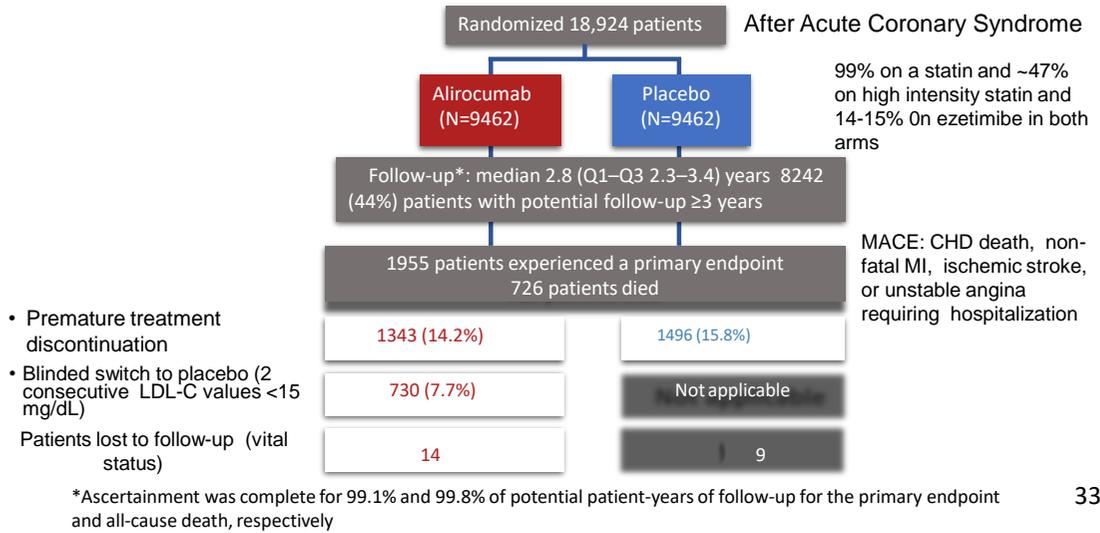
MI at 7 years: ARR 1.7%; NNT 59

Ischemic stroke at 7 years: 0.7%; NNT 142

'Modest' Benefit When Adding Ezetimibe to Statins in Post-ACS Patients. *Medscape*. Nov 17, 2014.

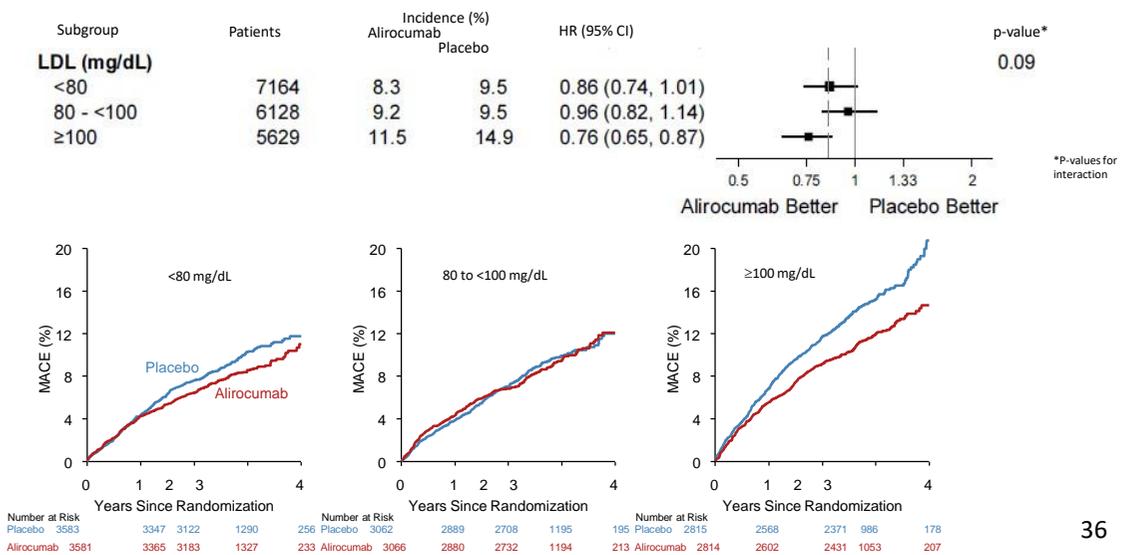
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ODYSSEY OUTCOMES Trial Patient Disposition



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Primary Efficacy in Main Prespecified Subgroups



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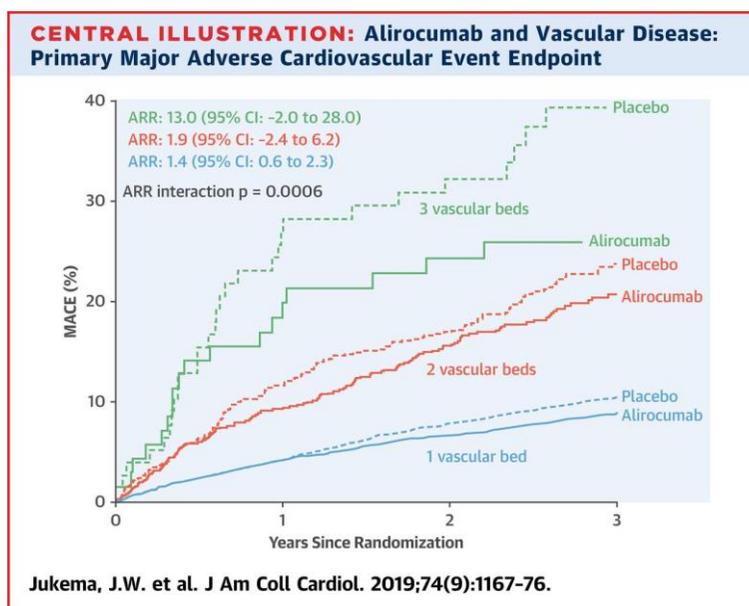
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Efficacy: Subgroup with Baseline LDL-C ≥ 100 mg/dL (Median Baseline LDL-C 118 mg/dL)

Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)/NNT	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4/30	0.76 (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0/100	0.72 (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3/77	0.69 (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7/59	0.71 (0.56, 0.90)

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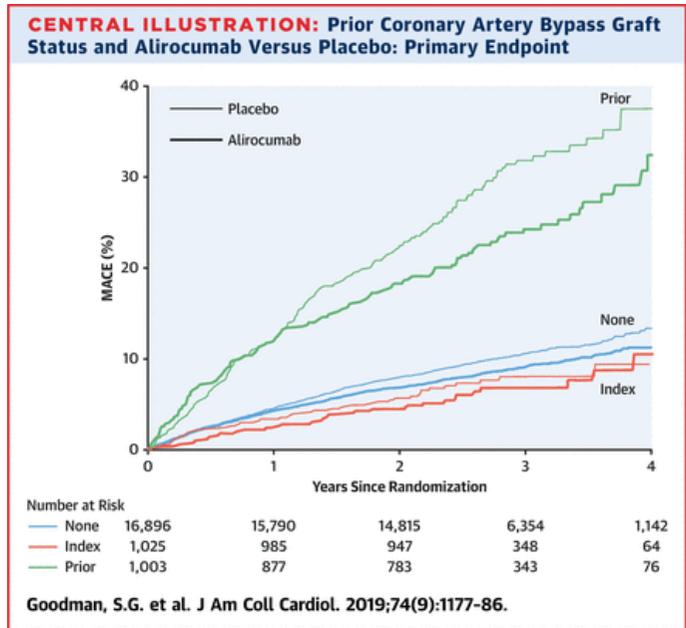


J. Wouter Jukema et al. J Am Coll Cardiol 2019;74:1167-1176



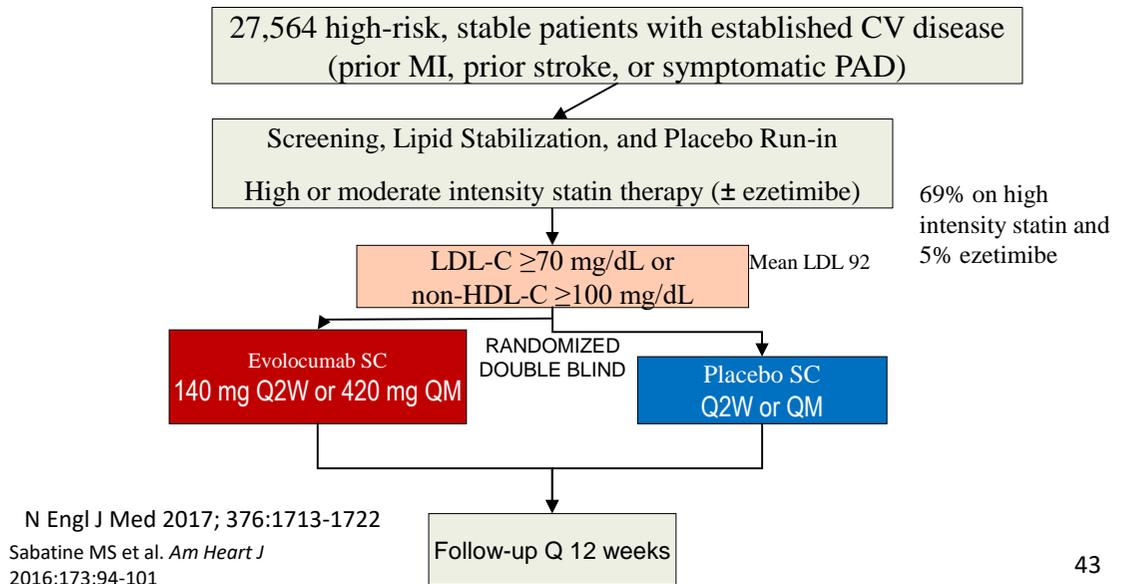
2019 The Authors

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Fourier Trial Design



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Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI) 3-yr Kaplan-Meier rate
	CVD, MI, stroke, UA, or revasc	12.6	
CV death, MI, or stroke	7.9	9.9	0.80 (0.73-0.88) NNT 50
Hosp for unstable angina	2.2	2.3	0.99 (0.82-1.18)
Coronary revasc	7.0	9.2	0.78 (0.71-0.86) NNT 46
Urgent	3.7	5.4	0.73 (0.64-0.83)
Elective	3.9	4.6	0.83 (0.73-0.95)
Death from any cause	4.8	4.3	1.04 (0.91-1.19)

N Engl J Med 2017; 376:1713-1722

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REDUCE-IT Trial with Icosapent ethyl (EPA, Vascepa)

- September 2018 Amarin/Kowa announced the topline results of the **Reduce-It Trial** a cardiovascular (CV) outcomes study of icosapent ethyl (VASCEPA) capsules met its pre-specified primary composite endpoint (4 point MACE of CV death, nonfatal myocardial infarction (MI, including silent MI), nonfatal stroke, coronary revascularization, and unstable angina requiring hospitalization) in the intent – to – treat population:
- Randomized **8,179** patients (~70% with ASCVD) on a 1:1 basis to statin plus VASCEPA 4g/day or statin plus placebo and compared the incidence of MACE between treatment arms over a median period of 4.9 years.
- Baseline LDL-C controlled to between 41-100 mg/dL (median baseline 75 mg/dL) by statin therapy and with various cardiovascular risk factors including persistent elevated TGs between 150-499 mg/dL (median baseline 216 mg/dL) and either established cardiovascular disease (secondary prevention) or diabetes mellitus and at least one other CV risk factor (primary prevention)
- Showed reduction in a composite of major adverse cardiovascular events (MACE) of approximately 25% – P value <0.001 (highly statistically significant)

• N Engl J Med 2019; 380:11-22

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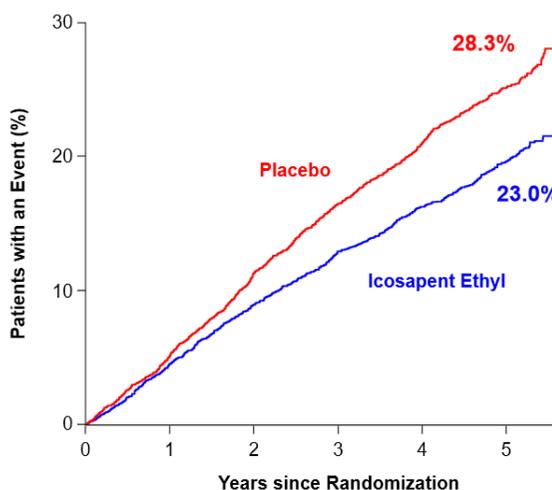
FDA - Approved Indication and Limitations of Use for VASCEPA

- Icosapent ethyl (VASCEPA) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (>500 mg/dL) hypertriglyceridemia.
- In patients with severe hypertriglyceridemia, the effect of icosapent ethyl on cardiovascular mortality or morbidity or on the risk of pancreatitis has not been determined.
- The daily dose of icosapent ethyl is 4 grams per day taken as four 0.5-gram capsules or two 1-gram capsules twice daily with food.
- Cost 1 Gm caps x 120 ~ \$242.00, 500 mg caps x 240 ~\$282.00
GoodRx.com 9/26/18

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Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75

(95% CI, 0.68–0.83)

RRR = 24.8%

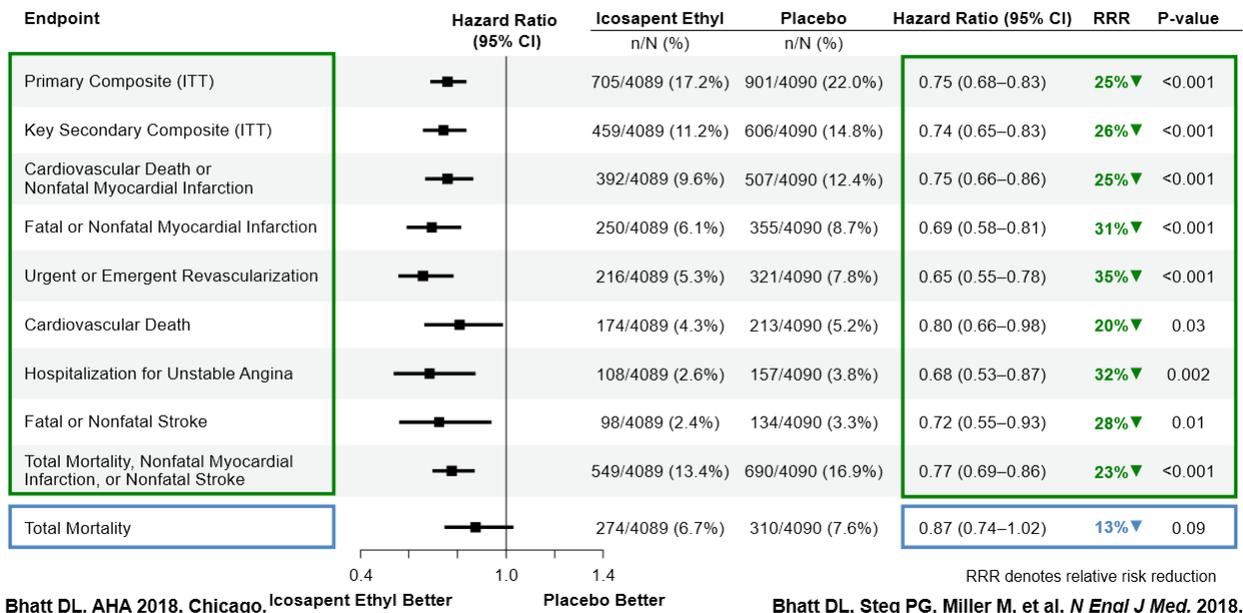
ARR = 4.8%

NNT = 21 (95% CI, 15–33)

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018. Bhatt DL. AHA 2018, Chicago.

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Prespecified Hierarchical Testing



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ADA 2019 Standards of Medical Care in Diabetes Update 3/28/2019

- Section 10, on cardiovascular disease and risk management, was revised to include a recommendation **based on the outcomes from the Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial (REDUCE-IT)** advising that icosapent ethyl be considered to reduce cardiovascular risk in patients with diabetes and atherosclerotic cardiovascular disease, or other cardiac risk factors, who are taking a statin and have controlled low-density lipoprotein cholesterol (LDL-C) but elevated triglycerides.
- The FDA granted priority review to Amarin's Vascepa with an Advisory Comm. hearing scheduled for late this year.

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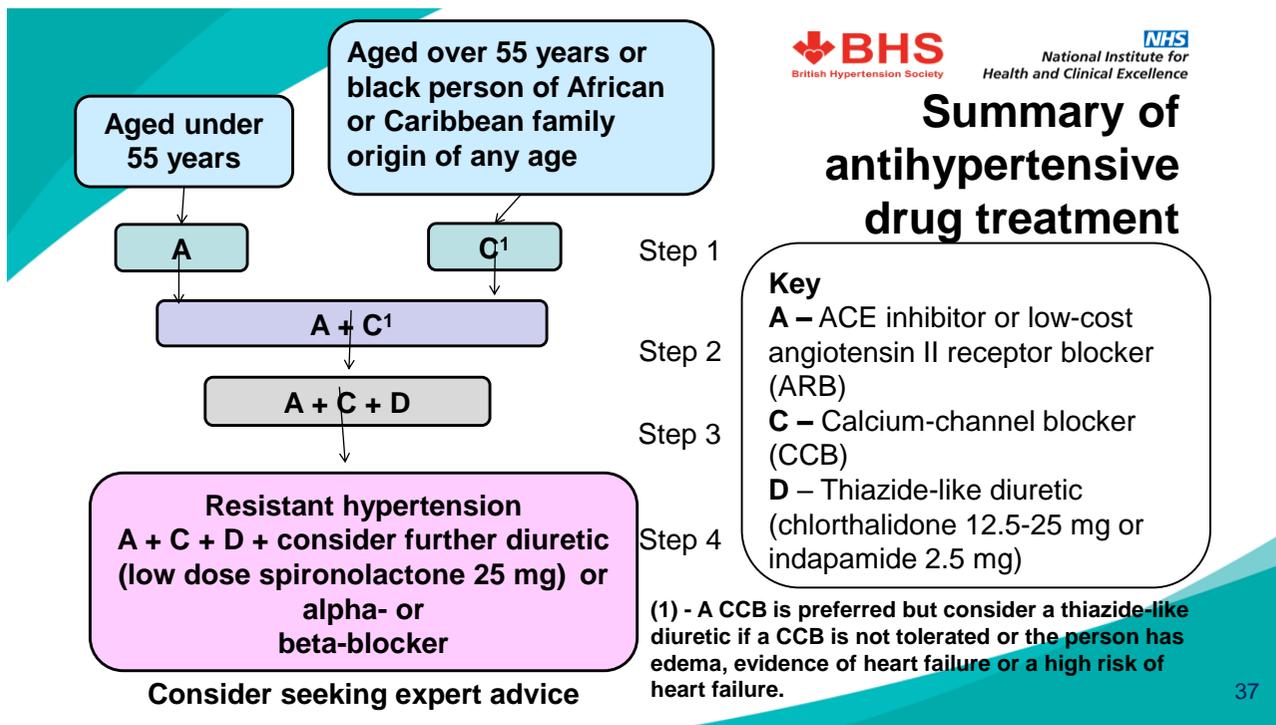
Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association Circulation. 2019;140:00–00. DOI: 10.1161/CIR.0000000000000709

- “We conclude that **prescription n-3 FAs, whether EPA+DHA or EPA-only, at a dose of 4 g/d, are clinically useful for reducing triglycerides**, after any underlying causes are addressed and diet and lifestyle strategies are implemented, **either as monotherapy or as an adjunct to other triglyceride-lowering therapies.**”
- “The use of n-3 FAs (4 g/d) for improving ASCVD risk in patients with HTG is supported by a 25% reduction in major adverse cardiovascular end points in REDUCEIT, a randomized placebo-controlled trial of EPA-only in high-risk patients on statin therapy. **Results from the STRENGTH trial, a randomized placebo-controlled cardiovascular outcomes trial of 4 g/d prescription EPA+DHA in patients with HTG and low HDL-C on statins, are anticipated in 2020.**”

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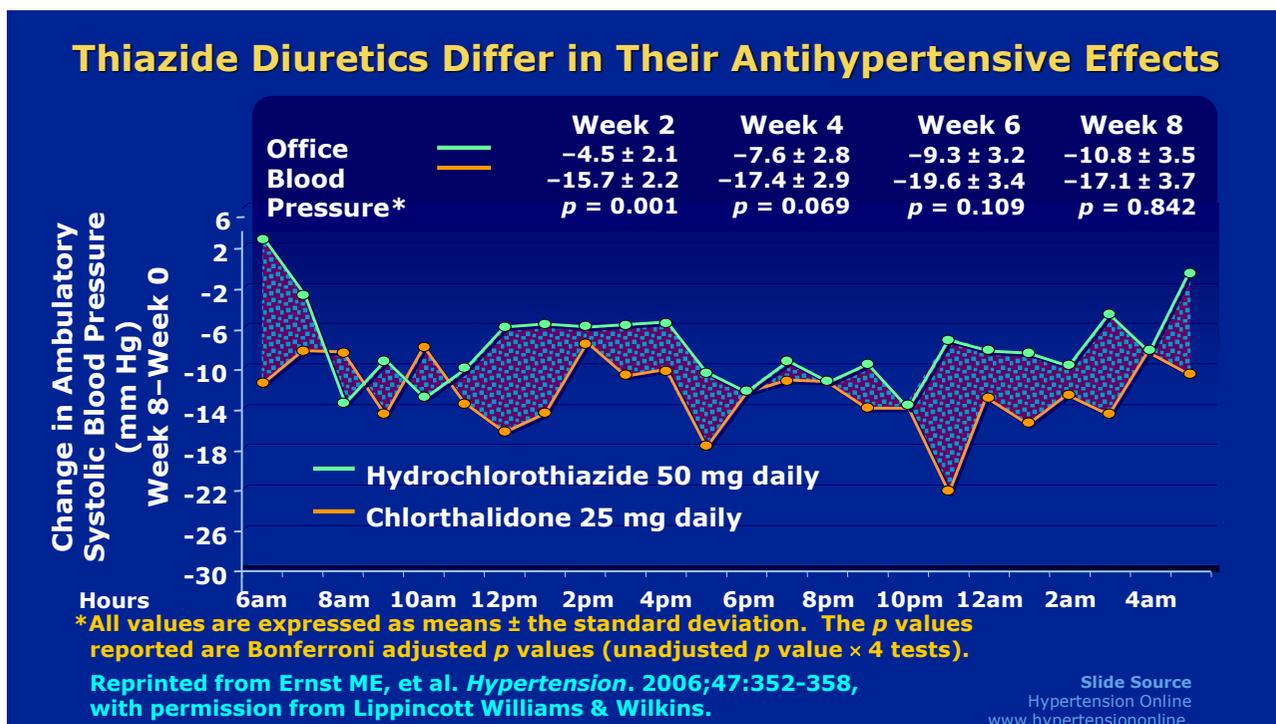
Which diuretic would you recommend for BP lowering?

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Indapamide vs. HCTZ in Patients with Impaired Renal Function and Hypertension

- **28 patients with impaired renal function and moderate hypertension.** The patients had elevated blood pressure for 2-27 years and impaired renal function for 1-15 years before entering the study. Their ages ranged between ,32-70 years and their **initial creatinine clearance was between 32 and 80 ml/min/1.73 m2 body surface area.** There were 16 female and 12 male patients. They were **randomly assigned for treatment with 2.5 mg of indapamide/day (14 patients) or with 50 mg of hydrochlorothiazide/day (14 patients) all patients were seen every 3 months and followed for 24 months.**
- **BP reductions were similar and maintained for the 24 months of follow-up**
 - (Am J Cardiol 1996;77:23B-25B)

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Indapamide vs. HCTZ in Patients with Impaired Renal Function and Hypertension

- **Creatinine clearance increased progressively in 13 of the 14 patients treated with indapamide; it rose from 58 +/- 4.4 to 72 +/- 4.4 ml/min/1.73 m2 body- surface area (p < 0.01) by the end of the treatment. In contrast, creatinine clearance fell progressively in 13 of the 14 patients who were managed with hydrochlorothiazide; it fell from 65 +/- 3.0 to 53 +/- 3.0 ml/min/1.73 m2 body surface area (p < 0.01) by the end of the study.**
- **Creatinine clearance increased by 28.5 +/- 4.4% with indapamide treatment and decreased by 17.4 +/- 3.0% with thiazide therapy, a statistically significant difference (p < 0.01).**
 - (Am J Cardiol 1996;77:23B-25B)

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Spironolactone for Hypertension. *Cochrane Database of Systematic Reviews 2010*

- **Meta-analysis of the 5 cross-over studies found a reduction in SBP of 20.09 mmHg (95%CI:16.58-23.06,p<0.00001) and a 6.75 mmHg (95%CI:4.8-8.69,p<0.00001) reduction in DBP.** These results were statistically significant and there was no evidence of heterogeneity between the studies. There may be a dose response effect with spironolactone up to 50 mg/day, but the confidence intervals around the mean end-of-study blood pressure for doses ranging 25-500 mg/day all overlapped.
- **In other words, it appears that doses >50mg/day do not produce further reductions in either SBP or DBP.**
- One cross-over study found that spironolactone 25 mg/day did not statistically significantly change SBP or DBP compared to placebo, SBP: -9.9 (95%CI:-21.15,1.35); DBP -2.34 (95%CI:-7.92,3.06).

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Diuretics

Cost and T1/2:

- **Chlorthalidone 25 and 50 mg tabs generic \$17-38.00/30 tabs**
 - T1/2: 40-60 hrs
- **Indapamide 1.25 and 2.5 mg tabs generic \$4-20.00/30 tabs**
 - T1/2: 14-26 hrs
- **Hydrochlorothiazide 12.5, 25 and 50 mg tabs generic \$4-11.00/30 tabs**
 - T1/2: 6-15 hrs
- **Spironolactone 25 and 50 mg tabs generic \$4-15.00/30 tabs**
 - T1/2: 1.4 – 16.5 hrs active metabolite
- **Eplerenone 25 and 50 mg tabs generic \$38-150.00/30 tabs**
 - T1/2: 3-6 hrs

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AHA Scientific Statement: Resistant Hypertension

- **Resistant hypertension (RH) is defined as above-goal elevated blood pressure (BP) in a patient despite the concurrent use of 3 antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic.**
- **Management of RH includes maximization of lifestyle interventions, use of or substitution of long-acting thiazide-like diuretics (chlorthalidone or indapamide), addition of a mineralocorticoid receptor antagonist (spironolactone or eplerenone), and, if BP remains elevated, stepwise addition of antihypertensive drugs with complementary mechanisms of action to lower BP. If BP remains uncontrolled, referral to a hypertension specialist is advised.**
 - (Hypertension. 2018;72:e53-e90).

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Efficacy and safety of once vs. twice daily dosing of lisinopril for hypertension

- Patients previously receiving lisinopril 20 mg were placed into the once- daily cohort if changed to **40 mg once daily or into the twice- daily cohort if changed to 20 mg twice daily**. Efficacy outcome measures were change in systolic blood pressure and diastolic blood pressure and achievement of blood pressure control (<140/90 mm Hg). **(Lisinopril the second most prescribed antihypertensive has a T1/2 of 12 hours)**
- Of 90 patients included (45 per cohort), the mean age was 61.8 years and 17.8% were black. **Once- and twice- daily administrations were associated with blood pressure reductions of 6.2/1.5 mm Hg and 16.5/5.9 mm Hg, with a 10.2/4.3 mm Hg greater reduction with twice- daily administration** (systolic blood pressure, P=.016; diastolic blood pressure, P=.068).
- **Twice- daily lisinopril dosing was associated with greater systolic blood pressure reductions compared with the same total daily dose administered once daily.**
 - J Clin Hypertens. 2017;19:868–873 (Univ of Colorado and Univ Florida)

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New 2019 GINA Asthma Guidelines April 12, 2019

Global Initiative for Asthma begun 1993 a joint effort between
NHLBI/NIH/WHO

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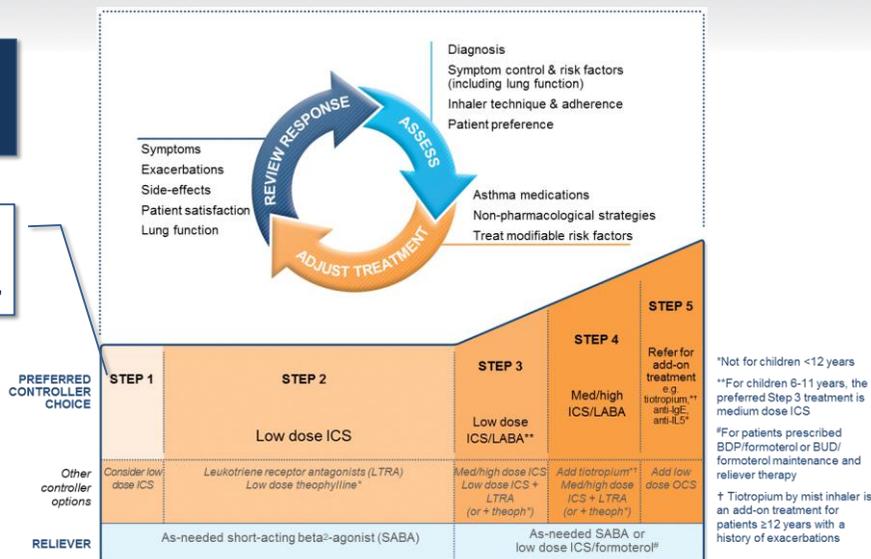
65

GINA 2018 – main treatment figure



Step 1 treatment is for patients with symptoms <twice/month and no risk factors for exacerbations

Previously, no controller was recommended for Step 1, i.e. SABA-only treatment was 'preferred'



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Background to changes in 2019 - the risks of SABA-only treatment



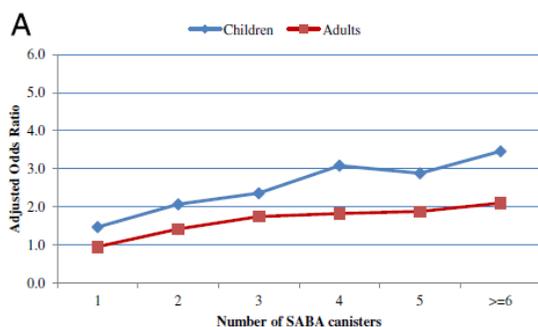
- **Regular or frequent use of SABA is associated with adverse effects**
 - β -receptor downregulation, decreased bronchoprotection, rebound hyperresponsiveness, decreased bronchodilator response (*Hancox, Respir Med 2000*)
 - Increased allergic response, and increased eosinophilic airway inflammation (*Aldridge, AJRCCM 2000*)
- **Higher use of SABA is associated with adverse clinical outcomes**
 - Dispensing of ≥ 3 canisters per year (average 1.7 puffs/day) is associated with higher risk of emergency department presentations (*Stanford, AAAI 2012*)
 - Dispensing of ≥ 12 canisters per year is associated with higher risk of death (*Suissa, AJRCCM 1994*)

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Short-acting beta-agonist use and its ability to predict future asthma-related outcomes

Medicaid

SABA – short-acting β -agonist

Commercial

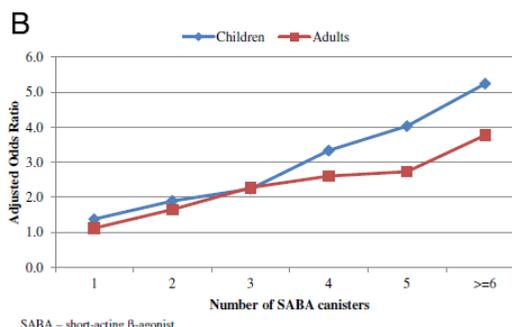
SABA – short-acting β -agonist

Fig. 1. (A) Odds of Asthma-related Hospitalization or emergency department visit by number of SABA canisters - Medicaid. (B) Odds of asthma-related hospitalization or emergency department visit by number of SABA canisters - Commercial.

Annals of Allergy, Asthma & Immunology 2012; 109:403-7

Each additional SABA canister resulted in an 8% to 14% and 14% to 18% increase in risk of an asthma-related exacerbation in children and adults, respectively.

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GINA 2019 – landmark changes in asthma management



- For safety, **GINA no longer recommends SABA-only treatment for Step 1**
 - This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any ICS significantly reduces the risk
- **GINA now recommends that all adults and adolescents with asthma should receive symptom-driven or regular low dose ICS-containing controller treatment, to reduce the risk of serious exacerbations**
 - This is a population-level risk reduction strategy, e.g. statins, anti-hypertensives

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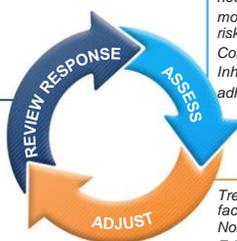
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Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

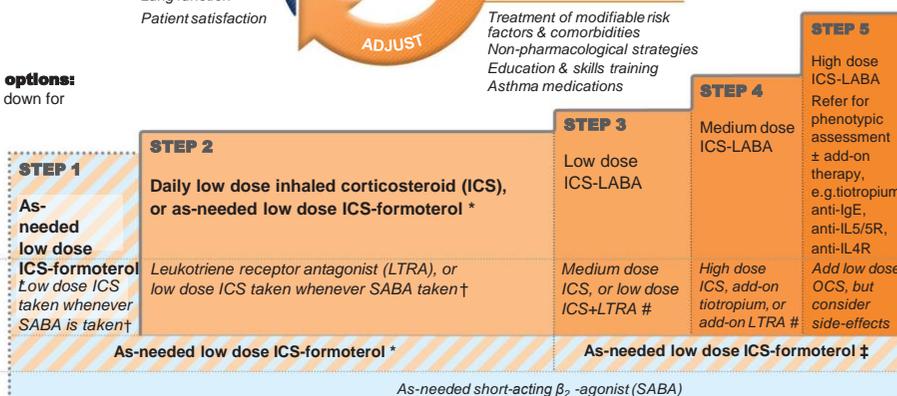
Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Asthma medication options:
Adjust treatment up and down for individual patient needs

PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

Other controller options

PREFERRED RELIEVER
Other reliever option



* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV₁ >70% predicted

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Step 2 – two ‘preferred’ controller options

As-needed low dose ICS-formoterol (off-label; all evidence with budesonide-formoterol)

- Evidence
 - Direct evidence from two large studies of non-inferiority for severe exacerbations vs daily low dose ICS + as-needed SABA (*O’Byrne, NEJMed 2018, Bateman, NEJMed 2018*)
 - **Direct evidence from one large study of 64% reduction in severe exacerbations vs SABA-only treatment (*O’Byrne, NEJMed 2018*)**
 - **Symptoms reduced; one study showed reduced exercise-induced bronchoconstriction**
- Values and preferences
 - High importance was given to preventing severe exacerbations, avoiding need for daily ICS in patients with mild or infrequent symptoms, and safety of as-needed ICS-formoterol in maintenance and reliever therapy, with no new safety signals
 - Lower importance given to small non-cumulative differences in symptom control (ACQ-5 difference 0.15 vs MCID 0.5) and lung function compared with daily ICS
 - Makes use of normal patient behavior (seeking symptom relief) to deliver controller

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Erenumab-aooe (Aimovig) by Amgen and Novartis

- **May 17, 2018 The U.S. Food and Drug Administration approved erenumab-aooe (Aimovig) for the preventive treatment of migraine in adults. The treatment is given by once-monthly self-injections. Erenumab-aooe is the first FDA-approved preventive migraine treatment in a new class of drugs that work by blocking the activity of calcitonin gene-related peptide, a molecule that is involved in migraine attacks.**
- **Erenumab is a human immunoglobulin G2 (IgG2) monoclonal antibody. Erenumab is specific and selective to CGRP receptors, exerting action by full competitive inhibition of the receptor.**

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FDA Updates Guidance on Nonproprietary Naming of Biological Products

- The FDA released updated guidance for **the “Nonproprietary Naming of Biological Products,”** originally released in January 2017. The updated guidance explains that:
- The FDA intends to designate a proper name that is a combination of the core name **and the distinguishing suffix that is devoid of meaning and composed of four lowercase letters**
 - Example - Erenumab-aooe (Aimovig)

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Erenumab-aooe (Aimovig)

- Pharmacokinetics: Median **time to peak concentration after subcutaneous administration of erenumab 1 mg to 210 mg ranged from 4 to 11 days (mean ~ 6 days).**
- The **estimated elimination half-life of erenumab in a typical 70 kg person receiving erenumab 70 mg subcutaneously is approximately 21 days.**
- **Erenumab-aooe is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.**

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Erenumab-aooe (Aimovig)

Table 5: Efficacy Endpoints at Month 3 in Study 3

Chronic Migraine	AIMOVIG 70 mg Once Monthly N = 188	AIMOVIG 140 mg Once Monthly N = 187	Placebo N = 281
Monthly Migraine Days (MMD)			
Change from baseline	-6.6	-6.6	-4.2
Difference from placebo	-2.5	-2.5	
<i>p</i> -value	< 0.001	< 0.001	
≥ 50% MMD responders			
% Responders	39.9%	41.2%	23.5%
Difference from placebo	16.4%	17.7%	
Odds ratio relative to placebo	2.2	2.3	
<i>p</i> -value	< 0.001	< 0.001	
Monthly acute migraine-specific medication days			
Change from baseline	-3.5	-4.1	-1.6
Difference from placebo	-1.9	-2.6	
<i>p</i> -value	< 0.001	< 0.001	

The Lancet Neurology Volume 16, Issue 6, June 2017, Pages 425-434

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Erenumab-aooe (Aimovig)

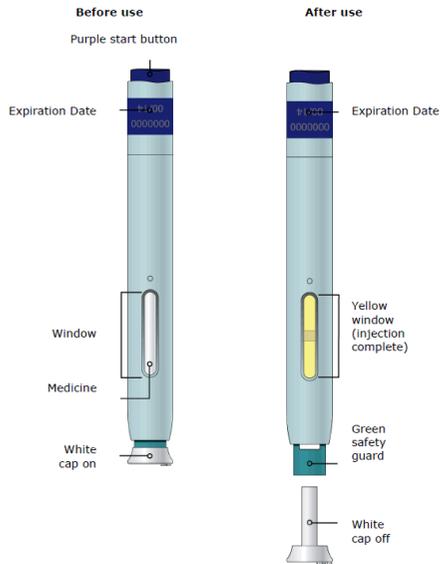
The autoinjector should be stored refrigerated at 2° C to 8° C (36° F to 46° F) in the original carton to protect from light until time of use (do not freeze or shake). Cost \$600.00 for 2 Sure Click
 Leave the autoinjector at room temperature for at least 30 minutes before injecting.
 If removed from the refrigerator, the autoinjector can be kept at room temperature in the original carton up (up to 25°C [77°F]) for up to 7 days.

The needle shield within the white cap of the AIMOVIG prefilled autoinjector and gray needle cap of the prefilled syringe contain dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex.

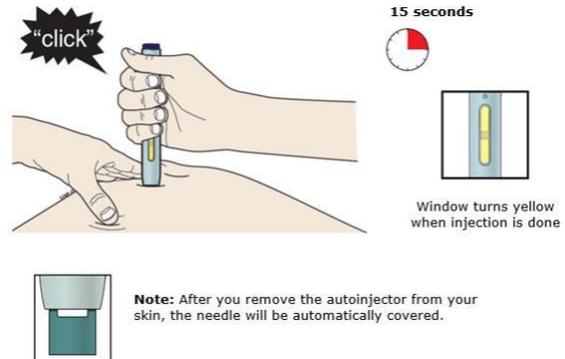


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Erenumab-aooe (Aimovig)



- Cost \$600.00 for 2 SureClick autoinjector



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Erenumab-aooe (Aimovig)

- In a **1-year open-label extension study in 451 patients with chronic migraine**, patients taking 140 mg and 70 mg of erenumab **experienced reductions of average monthly migraine days of 10.5 days and 8.5 days, respectively, compared to a baseline of 18.1 days. Patients treated with Aimovig experienced reductions in monthly migraine days of:**
 - **50 percent or more: 67 percent on 140 mg and 53 percent on 70 mg**
 - **75 percent or more: 42 percent on 140 mg and 27 percent on 70 mg**
 - **100 percent reduction: 13 percent on 140 mg and 6 percent on 70 mg**
- Amgen press release 6/28/2018

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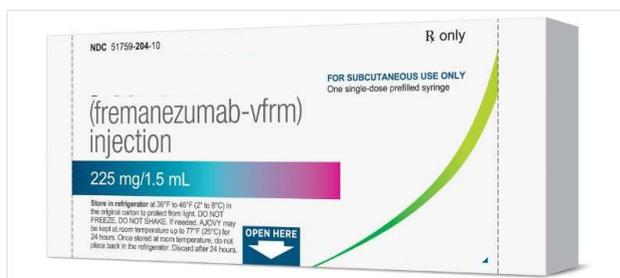
Fremanezumab-vfrm (Ajovy) by Teva

- 9/14/18 FDA approved Fremanezumab-vfrm for the prevention of migraines in adults.
- A fully humanized IgG2Δa/kappa monoclonal antibody specific for calcitonin gene-related peptide (CGRP) ligand that binds to the CGRP ligand and blocks its binding to the receptor. Fremanezumab-vfrm is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.
- **Recommended Dosage:** Two subcutaneous dosing options of fremanezumab-vfrm are available to administer the recommended dosage:
 - 225 mg monthly, (available in 225 mg/1.5 mL single-dose prefilled syringe) or
 - 675 mg every 3 months (quarterly), which is administered as three consecutive subcutaneous injections of 225 mg each. Cost ~\$400.00/prefilled syringe

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Fremanezumab-vfrm (Ajovy)

- Remove fremanezumab-vfrm/AJOVY from the refrigerator. Prior to use, allow the medication to sit at room temperature for 30 minutes protected from direct sunlight. Do not warm by using a heat source such as hot water or a microwave. Do not use if it has been at room temperature for 24 hours or longer.



AJOVY prefilled syringe (Before use). See Figure A.

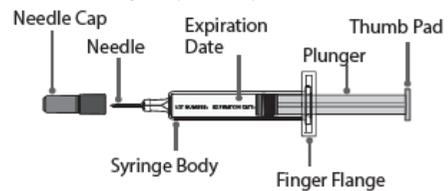


Figure A

AJOVY prefilled syringe (After use). See Figure B.



Figure B

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Fremanezumab-vfrm (Ajovy)

- After single subcutaneous (SC) administrations of 225 mg, 675 mg, and 900 mg fremanezumabvfrm, median time to maximum concentrations (t_{max}) was 5 to 7 days. Dose-proportionality, based on population PK, was observed between 225 mg to 900 mg. Steady state was achieved by approximately 168 days (about 6 months) following 225 mg SC monthly and 675 mg SC quarterly dosing regimens.
- Fremanezumab-vfrm was estimated to have a half-life of approximately 31 days.
- Fremanezumab is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

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Fremanezumab-vfrm (Ajovy)

Table 2: Efficacy Endpoints in Study 1

Study 1 Efficacy Endpoint Episodic Migraine	AJOVY 225 mg Monthly (N=287)	AJOVY 675 mg Quarterly (N=288)	Placebo (N=290)
Monthly migraine days (MMD)			
Baseline migraine days	8.9	9.2	9.1
Change from baseline	-3.7	-3.4	-2.2
Difference from placebo	-1.5	-1.2	
p-value	<0.001	<0.001	
≥50% MDD responders			
% responders	47.7%	44.4%	27.9%
Difference from placebo	19.8%	16.5%	
p-value	<0.001	<0.001	
Monthly acute migraine-specific medication days			
Change from baseline	-3.0	-2.9	-1.6
Difference from placebo	-1.4	-1.3	
p-value	<0.001	<0.001	

Figure 1 displays the mean change from baseline in the average monthly number of migraine days in Study 1.

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Fremanezumab-vfrm (Ajovy)

Table 3: Efficacy Endpoints in Study 2

Study 2 Efficacy Endpoint Chronic Migraine	AJOVY 225 mg ^a Monthly (N=375)	AJOVY 675 mg Quarterly (N=375)	Placebo (N=371)
Baseline headache days of any severity ^b	20.3	20.4	20.3
Baseline headache days of at least moderate severity ^c	12.8	13.2	13.3
Change from baseline in the monthly average number of headache days of at least moderate severity	-4.6	-4.3	-2.5
Difference from placebo	-2.1	-1.8	
p-value	<0.001	<0.001	
Change from baseline in the monthly average number of migraine days in patients	-5.0	-4.9	-3.2
Change from baseline in monthly average number of headache days of at least moderate severity at 4 weeks after 1 st dose	-4.6	-4.6	-2.3
Percentage of patients with \geq 50% reduction in monthly average number of headache days of at least moderate severity	40.8%	37.6%	18.1%
Change from baseline in monthly average number of days of acute headache medication	-4.2	-3.7	-1.9

^a In Study 2, patients received a 675 mg starting dose.

^b Used for chronic migraine diagnosis.

^c Used for primary endpoint analysis.

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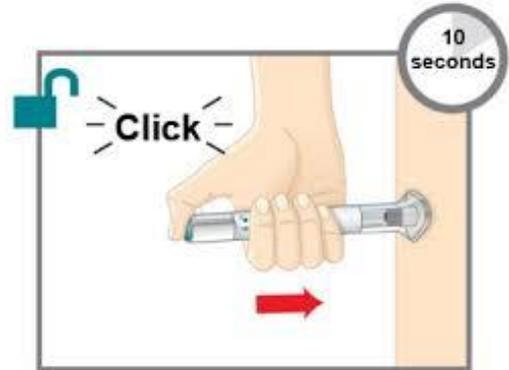
Fremanezumab-vfrm (Ajovy)

- **The most common adverse reactions were at the injection site (eg, injection-site pain, injection-site erythema), and occurred in 47% of the group receiving fremanezumab quarterly, 47% of those receiving fremanezumab monthly, and 40% of the placebo group.** The most common adverse event was injection-site pain, which occurred in 30% of the fremanezumab quarterly group, 26% of the fremanezumab monthly group, and 28% of the placebo group
- **Hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with fremanezumab in clinical trials.** Most reactions were mild to moderate, but some led to discontinuation or required corticosteroid treatment. Most reactions were reported from within hours to one month after administration.

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Galcanezumab-gnlm (Emgality) by Lilly

- 9/27/18 FDA approved galcanezumab-gnlm for the prevention of migraines in adults. A humanized IgG4 monoclonal antibody specific for calcitonin-gene related peptide (CGRP) ligand and blocks its binding to the receptor. (Note-only the 120 mg dose after a loading dose of 240 mg is FDA approved)



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Galcanezumab-gnlm (Emgality)

Pharmacokinetics:

- **The time to maximum concentration is 5 days, and the elimination half-life is 27 days.**
- Galcanezumab-gnlm is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.
- The pharmacokinetics of galcanezumab-gnlm were **not affected by age, sex, race, or subtypes of migraine spectrum (episodic or chronic migraine)**, based on a population pharmacokinetics analysis. **Body weight has no clinically relevant effect** on the pharmacokinetics of galcanezumab-gnlm.
- **Renal and hepatic impairment are not expected to affect the pharmacokinetics of galcanezumab-gnlm.**
- **Galcanezumab-gnlm is not metabolized by cytochrome P450 enzymes;** therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

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Galcanzumab-gnlm (Emgality)

Table 2: Efficacy Endpoints in Studies 1 and 2

Episodic Migraine	Study 1		Study 2	
	EMGALITY 120 mg N = 210	Placebo N = 425	EMGALITY 120 mg N = 226	Placebo N = 450
Monthly Migraine Headache Days (over Months 1 to 6)				
Baseline migraine headache days	9.2	9.1	9.1	9.2
Mean change from baseline	-4.7	-2.8	-4.3	-2.3
Difference from placebo*	-1.9		-2.0	
≥50% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders*	62%	39%	59%	36%
≥75% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders*	39%	19%	34%	18%
100% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders*	16%	6%	12%	6%
Monthly Migraine Headache Days that Acute Medication was Taken (over Months 1 to 6)				
Mean change from baseline (days)*	-4.0	-2.2	-3.7	-1.9
MSQ Role Function-Restrictive Domain Score (over Months 4 to 6)				
Baseline	51.4	52.9	52.5	51.4
Mean change from baseline ^a	32.4	24.7	28.5	19.7
Difference from placebo*	7.7		8.8	

^a N = 189 for EMGALITY 120 mg and N = 377 for placebo in Study 1; N = 213 for EMGALITY 120 mg and N = 396 for placebo in Study 2.

* p<0.001

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Galcanzumab-gnlm (Emgality)

Table 3: Efficacy Endpoints in Study 3

Chronic Migraine	EMGALITY 120 mg N = 273	Placebo N = 538
Monthly Migraine Headache Days (over Months 1 to 3)		
Baseline migraine headache days	19.4	19.6
Mean change from baseline	-4.8	-2.7
Difference from placebo*	-2.1	
≥50% Migraine Headache Days Responders (over Months 1 to 3)		
% Responders*	28%	15%

^a N = 252 for EMGALITY 120 mg and N = 494 for placebo.

* p<0.001

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Galcanezumab-gnlm (Emgality)

- **Adverse Effects: Injection site reactions (18% galcanezumab vs. 13% placebo)** include multiple related adverse event terms, such as injection site pain, injection site reaction, injection site erythema, and injection site pruritus. **Hypersensitivity reactions (e.g., rash, urticaria, and dyspnea) have been reported**
- **Immunogenicity: With 12 months of treatment in an open-label study, up to 12.5% (16/128) of galcanezumab-treated patients developed anti-galcanezumab-gnlm antibodies, most of whom tested positive for neutralizing antibodies.**
- Although anti-galcanezumab-gnlm antibody development was **not found to affect the pharmacokinetics, safety, or efficacy of galcanezumab in these patients, the available data are too limited to make definitive conclusions.**

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Galcanezumab-gnlm – Emgality

- March 2019 the Food and Drug Administration “**granted Priority Review for the supplemental Biologics License Application (sBLA) for galcanezumab (Emgality) for the prevention/treatment of episodic cluster headache in adults**
- **Cluster headache** is a form of headache that produces extreme pain and tends to occur in clusters, often at the same time(s) of the day, for several weeks to months. The headaches are accompanied by symptoms that may include: **bloodshot eyes, excessive tearing of the eyes, drooping of the eyelids, runny nose and/or nasal congestion and facial sweating.** Some people experience restlessness and agitation. **Cluster headache attacks may strike several times a day, generally lasting between 15 minutes and three hours.**

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Galcanezumab-gnlm – Emgality

- June 4, 2019 The FDA approved Emgality for the treatment of cluster headaches. The FDA said **“Emgality provides patients with the first FDA-approved drug that reduces the frequency of attacks of episodic cluster headache, an extremely painful and often debilitating condition,”**
- **Episodic cluster headache recommended dosage: 300 mg (administered as three consecutive injections of 100 mg each) at the onset of the cluster period, and then monthly until the end of the cluster period.**

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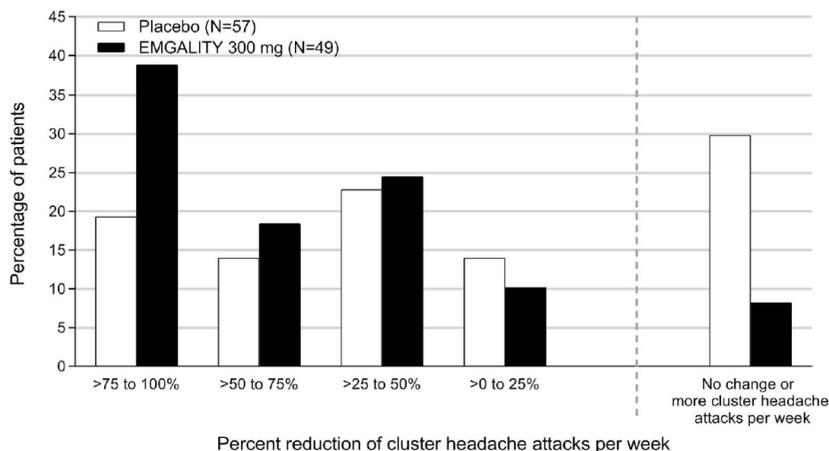
Galcanezumab-gnlm – Emgality

	EMGALITY 300 mg N = 49	Placebo N = 57
Mean Reduction in Weekly Cluster Headache Attack Frequency (over Weeks 1 to 3)		
Prospective Baseline Cluster Headache Attack Frequency	17.8	17.3
Mean change from baseline	-8.7	-5.2
Difference from placebo	-3.5	
p-value	0.036	
≥50% Weekly Cluster Headache Attack Frequency Responders (at Week 3)		
% Responders	71.4%	52.6%
Difference from placebo	18.8%	
p-value	0.046	

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Galcanzumab-gnlm – Emgality

Figure 8: Distribution of the Average Percent Change from Baseline in Weekly Cluster Headache Attack Frequency over Weeks 1 to 3 in Study 4¹

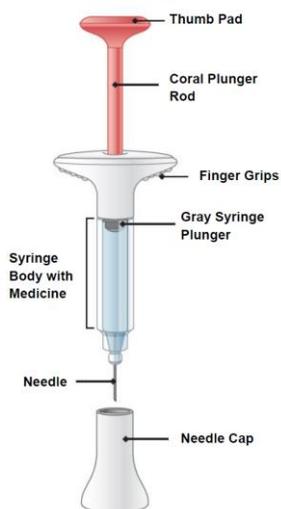


¹ N = number of intent to treat patients with non-missing average percentage change from baseline in weekly cluster headache attack frequency over weeks 1 to 3.

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Galcanzumab-gnlm – Emgality

EMGALITY Prefilled Syringe



Storage and Handling:

- Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect Emgality from light until use.
- Do not freeze.
- Do not shake.
- Emgality may be stored out of refrigeration in the original carton at temperatures up to 30°C (86°F) for up to 7 days. Once stored out of refrigeration, do not place back in the refrigerator.

Dosage: 300 mg (three consecutive subcutaneous injections of 100 mg each) at the onset of the cluster period, and then monthly until the end of the cluster period.

Cost: reported to be the same cost per mg as existing products?

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Investigational Oral CGRP Antagonists “gepants”

- The oral calcitonin gene-related peptide antagonist ubrogepant has been submitted to the FDA and the PDUFA data is scheduled for the fourth quarter of 2019, according to an Allergan press release.
- Data from 3,358 patients with migraine (with and without aura) randomized in an approximate 1:1:1:1 ratio to receive either a 25-mg dose, 50-mg dose or 100-mg dose of ubrogepant (Allergan) or placebo. Patients were labeled as triptan-effective, triptan-ineffective or triptan-naive based on previous treatment attempts. Results found across all subgroups, those who received ubrogepant had higher response rates for 2-hour pain freedom and most bothersome pain symptom.
- **Atogepant and Rimegepant – for both treatment and prevention**
 - American Headache Society Annual Scientific Meeting; July 11-14, 2019; Philadelphia.

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The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice

- Measuring the response to anti-CGRP mAbs will be patient- and healthcare professional dependent and will be guided by the same outcome metrics described previously for preventive treatments, with emphasis on migraine/headache days, migraine-related disability, impact, and functional impairment.
- Measuring outcomes for patients on mAbs and making a decision regarding continuation requires 3 months of outcome data for patients receiving monthly injections or 6 months of follow-up for a treatment designed for quarterly injection or infusion.
 - a significant proportion of patients who do not achieve at least a 50% reduction in MHDs in the 4 weeks after the first SC dose may achieve a response in the 4 weeks after a second dose. Similarly, a smaller yet significant proportion of patients will respond in 4 to 8 weeks after a third consecutive SC dose.

Headache 2019;59:1-18

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The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice

Table 6.—Criteria for Continuation of Monoclonal Antibodies to Calcitonin Gene-Related Peptide or Its Receptor or Neuromodulation Therapy[†]

Reauthorization after initial use [‡] is approved when EITHER of the following criteria are met:	
1. Reduction in mean monthly headache days of ≥50% relative to the pretreatment baseline (Diary documentation or healthcare provider attestation)	
2. A clinically meaningful improvement in ANY of the following validated migraine-specific patient-reported outcome measures:	
a. MIDAS	
i. Reduction of ≥5 points when baseline score is 11–20	
ii. Reduction of ≥30% when baseline scores >20	
b. MPFID	
i. Reduction of ≥5 points	
c. HIT-6	
i. Reduction of ≥5 points	

HIT, Headache Impact Test; MHD, monthly headache day; MIDAS, Migraine Disability Assessment; MPFID, Migraine Physical Function Impact Diary.

Reauthorization duration: Indefinite; guided by patient response and healthcare provider attestation.

[†]Exceptions to these criteria may be made under circumstances when deemed medically indicated by the prescribing licensed healthcare provider.

[‡]Initial authorization: 3 months for treatments administered monthly; for treatments delivered quarterly (every 3 months), 2 cycles of treatment (6 months).

Headache 2019;59:1-18

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Diagnosis and Treatment of Adults with Community-acquired Pneumonia - Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

Table 2. Differences between the 2019 and 2007 American Thoracic Society/Infectious Diseases Society of America Community-acquired Pneumonia Guidelines

Recommendation	2007 ATS/IDSA Guideline	2019 ATS/IDSA Guideline
Sputum culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or <i>Pseudomonas aeruginosa</i>
Blood culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or <i>P. aeruginosa</i>
Macrolide monotherapy	Strong recommendation for outpatients	Conditional recommendation for outpatients based on resistance levels
Use of procalcitonin	Not covered	Not recommended to determine need for initial antibacterial therapy
Use of corticosteroids	Not covered	Recommended not to use. May be considered in patients with refractory septic shock
Use of healthcare-associated pneumonia category	Accepted as introduced in the 2005 ATS/IDSA hospital-acquired and ventilator-associated pneumonia guidelines	Recommend abandoning this categorization. Emphasis on local epidemiology and validated risk factors to determine need for MRSA or <i>P. aeruginosa</i> coverage. Increased emphasis on deescalation of treatment if cultures are negative
Standard empiric therapy for severe CAP	β-lactam/macrolide and β-lactam/fluoroquinolone combinations given equal weighting	Both accepted but stronger evidence in favor of β-lactam/macrolide combination
Routine use of follow-up chest imaging	Not addressed	Recommended not to obtain. Patients may be eligible for lung cancer screening, which should be performed as clinically indicated

Definition of abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*.

Am J Respir Crit Care Med 2019; 200: e45-e67

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Diagnosis and Treatment of Adults with Community-acquired Pneumonia - Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

Table 3. Initial Treatment Strategies for Outpatients with Community-acquired Pneumonia

Standard Regimen	
No comorbidities or risk factors for MRSA or <i>Pseudomonas aeruginosa</i> ^a	Amoxicillin or doxycycline or macrolide (if local pneumococcal resistance is <25%) [†]
With comorbidities [‡]	Combination therapy with amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline [§] OR monotherapy with respiratory fluoroquinolone

Definition of abbreviations: ER = extended release; MRSA = methicillin-resistant *Staphylococcus aureus*.

^aRisk factors include prior respiratory isolation of MRSA or *P. aeruginosa* or recent hospitalization AND receipt of parenteral antibiotics (in the last 90 d).

[†]Amoxicillin 1 g three times daily, doxycycline 100 mg twice daily, azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, or clarithromycin ER 1,000 mg daily.

[‡]Comorbidities include chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia.

[§]Amoxicillin/clavulanate 500 mg/125 mg three times daily, amoxicillin/clavulanate 875 mg/125 mg twice daily, 2,000 mg/125 mg twice daily, cefpodoxime 200 mg twice daily, or cefuroxime 500 mg twice daily; AND azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, clarithromycin ER 1,000 mg daily, or doxycycline 100 mg twice daily.

^{||}Levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily.

Am J Respir Crit Care Med 2019; 200: e45-e67

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Treatment of Adults with Community-acquired Pneumonia Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

- In the Outpatient Setting, which Antibiotics Are Recommended for Empiric Treatment of CAP in Adults?
 1. For healthy outpatient adults without comorbidities listed below or risk factors for antibiotic resistant pathogens, we recommend:
 - amoxicillin 1 g three times daily (strong recommendation, moderate quality of evidence), or
 - doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence), or
 - a macrolide (azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin extended release 1,000 mg daily) only in areas with pneumococcal resistance to macrolides ,25% (conditional recommendation, moderate quality of evidence).

Am J Respir Crit Care Med 2019; 200: e45-e67

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Treatment of Adults with Community-acquired Pneumonia

Clinical Practice Guideline of the American Thoracic Society and
Infectious Diseases Society of America

2. For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia we recommend (in no particular order of preference):

- Combination therapy: amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefepodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy), or doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence for combination therapy); OR Monotherapy: respiratory fluoroquinolone (levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily) (strong recommendation, moderate quality of evidence).
 - Am J Respir Crit Care Med 2019; 200: e45-e67

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Treatment of Adults with Community-acquired Pneumonia

Clinical Practice Guideline of the American Thoracic Society and
Infectious Diseases Society of America

- In the Inpatient Setting, Which Antibiotic Regimens Are Recommended for Empiric Treatment of CAP in Adults without Risk Factors for MRSA and *P. aeruginosa*?
 - In inpatient adults with nonsevere CAP without risk factors for MRSA or *P. aeruginosa*, we recommend the following empiric treatment regimens (in no order of preference)
 - combination therapy with a b-lactam (ampicillin+sulbactam 1.5–3 g every 6 h, cefotaxime 1–2 g every 8 h, ceftriaxone 1–2 g daily, or ceftaroline 600 mg every 12 h) and a macrolide (azithromycin 500 mg daily or clarithromycin 500 mg twice daily) (strong recommendation, high quality of evidence), or
 - monotherapy with a respiratory fluoroquinolone (levofloxacin 750 mg daily, moxifloxacin 400 mg daily) (strong recommendation, high quality of evidence).
 - A third option for adults with CAP who have contraindications to both macrolides and fluoroquinolones is: combination therapy with a b-lactam (ampicillin+sulbactam, cefotaxime, ceftaroline, or ceftriaxone, doses as above) and doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence). Am J Respir Crit Care Med 2019; 200: e45-e67

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Treatment of Adults with Community-acquired Pneumonia

Clinical Practice Guideline of the American Thoracic Society and
Infectious Diseases Society of America

- In inpatient adults with severe CAP without risk factors for MRSA or *P. aeruginosa*, we recommend:
 - a b-lactam plus a macrolide (strong recommendation, moderate quality of evidence); or
 - a b-lactam plus a respiratory fluoroquinolone (strong recommendation, low quality of evidence).
- In the Inpatient Setting, Should Patients with Suspected Aspiration Pneumonia Receive Additional Anaerobic Coverage beyond Standard Empiric Treatment for CAP?
 - Recommendation. We suggest not routinely adding anaerobic coverage for suspected aspiration pneumonia unless lung abscess or empyema is suspected (conditional recommendation, very low quality of evidence).
 - Am J Respir Crit Care Med 2019; 200: e45-e67

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Treatment of Adults with Community-acquired Pneumonia

Clinical Practice Guideline of the American Thoracic Society and
Infectious Diseases Society of America

- In the Inpatient Setting, Should Adults with CAP and Risk Factors for MRSA or *P. aeruginosa* Be Treated with Extended-Spectrum Antibiotic Therapy Instead of Standard CAP Regimens?
 - Recommendation. We recommend abandoning use of the prior categorization of healthcare-associated pneumonia (HCAP) to guide selection of extended antibiotic coverage in adults with CAP (strong recommendation, moderate quality of evidence) - only cover empirically for MRSA or *P. aeruginosa* in adults with CAP if locally validated risk factors for either pathogen are present.
 - residence in a nursing home and other long-term care facilities, hospitalization for >2 days in the last 90 days, receipt of home infusion therapy, chronic dialysis, home wound care, or a family member with a known antibiotic-resistant pathogen.
 - Am J Respir Crit Care Med 2019; 200: e45-e67

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Treatment of Adults with Community-acquired Pneumonia

Clinical Practice Guideline of the American Thoracic Society and
Infectious Diseases Society of America

- We recommend clinicians only cover empirically for MRSA or *P. aeruginosa* in adults with CAP if locally validated risk factors for either pathogen are present (strong recommendation, moderate quality of evidence).
 - Empiric treatment options for MRSA include vancomycin (15 mg/kg every 12 h, adjust based on levels) or linezolid (600 mg every 12 h).
 - Empiric treatment options for *P. aeruginosa* include piperacillin-tazobactam (4.5 g every 6 h), cefepime (2 g every 8 h), ceftazidime (2 g every 8 h), aztreonam (2 g every 8 h), meropenem (1 g every 8 h), or imipenem (500 mg every 6 h).
 - Am J Respir Crit Care Med 2019; 200: e45-e67

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Treatment of Adults with Community-acquired Pneumonia

Clinical Practice Guideline of the American Thoracic Society and
Infectious Diseases Society of America

- In the Inpatient Setting, Should Adults with CAP Be Treated with Corticosteroids?
 - We recommend not routinely using corticosteroids in adults with nonsevere CAP (strong recommendation, high quality of evidence).
 - We suggest not routinely using corticosteroids in adults with severe CAP (conditional recommendation, moderate quality of evidence).
 - We suggest not routinely using corticosteroids in adults with severe influenza pneumonia (conditional recommendation, low quality of evidence).
 - We endorse the Surviving Sepsis Campaign recommendations on the use of corticosteroids in patients with CAP and refractory septic shock
 - Am J Respir Crit Care Med 2019; 200: e45-e67

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Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout (NEJM on-line 3-12-2018)

- 6190 patients underwent randomization, received febuxostat or allopurinol, and were followed for a median of 32 months (maximum, 85 months). CARES Trial
- In the modified intention-to-treat analysis, a **primary end-point (the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization for unstable angina)** event occurred in 335 patients (10.8%) in the febuxostat group and in 321 patients (10.4%) in the allopurinol group (hazard ratio, 1.03; upper limit of the one-sided 98.5% confidence interval [CI], 1.23; P=0.002 for noninferiority).
- **All-cause and cardiovascular mortality were higher in the febuxostat group than in the allopurinol group (hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]; hazard ratio for cardiovascular death 1.34 [95% CI, 1.03 to 1.73]), febuxostat 134 cases (4.3%) vs. allopurinol 100 cases (3.2%) RRI 34%, ARI 1.1%, NNH 91.**

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New Black Box Warning for Febuxostat (Uloric)

- . [2-21-2019] The U.S. Food and Drug Administration (FDA) has concluded there is **an increased risk of death with febuxostat (Uloric) compared to another gout medicine, allopurinol**. This conclusion is based on our in-depth review of results from a safety clinical trial that found an increased risk of heart-related death and death from all causes with febuxostat.
- **FDA is requiring a Black Box Warning and limiting the approved use of febuxostat to certain patients who are not treated effectively or experience severe side effects with allopurinol.**
- **Counsel patients to seek medical attention immediately if they experience chest pain, shortness of breath, rapid or irregular heartbeat, numbness or weakness on one side of the body, dizziness, trouble talking, or a sudden severe headache while taking febuxostat**

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New Black Box Warning for Hypnotics

- [04-30-2019] The Food and Drug Administration (FDA) is advising that **rare but serious injuries have happened with certain common prescription insomnia medicines because of sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors have also resulted in deaths.** These behaviors appear to be more common with eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist) than other prescription medicines used for sleep.

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New Black Box Warning for Hypnotics

- Between December 16, 1992, and March 13, 2018. Of the **66 cases, 20 cases were reported as resulting in fatal outcomes. Forty-six cases reported serious non-fatal injuries; these patients usually did not remember experiencing these complex sleep behaviors.**
- The adverse events included falls (n=22) with serious injuries such as intracranial hemorrhages, vertebral fractures, and hip fractures. Other events included self-injuries (n=7), fatal falls (n=6), accidental overdoses (n=5), hypothermia (n=5), suicide attempts (n=5), apparent completed suicides (n=4), fatal motor vehicle collisions (n=4), gunshot wounds (n=3), carbon monoxide poisoning (2), drowning or near drowning (n=2), burns (n=2), and homicide (n=1).

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Oral Semaglutide – Rybelsus by Novo Nordisk

- 9/20/2019 The FDA approved the **first oral GLP-1 agonist oral semaglutide** – Rybelsus by Novo-Nordisk.
- Rybelsus (semaglutide) tablets 7 mg or 14 mg once a day is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.
- **Tablets 3 mg, 7 mg and 14 mg**
- **Cost: list price of \$26 per day, or \$772 per 30 tablets across all doses—a price that’s “in-line with injectables” from that same class.**

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Oral Semaglutide – Rybelsus

BOX WARNING: RISK OF THYROID C-CELL TUMORS

- In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether RYBELSUS® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined
- RYBELSUS® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of RYBELSUS® and **inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness)**. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with RYBELSUS®

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Oral Semaglutide – Rybelsus

Limitations of Use:

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.
- **Has not been studied in patients with a history of pancreatitis.**
 - **After initiation of oral semaglutide, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting).** If pancreatitis is suspected, oral semaglutide should be discontinued.
- Not indicated for use in patients with type 1 diabetes mellitus or treatment of diabetic ketoacidosis.

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Oral Semaglutide – Rybelsus

- **Once-daily tablet formulated with SNAC**
- SNAC (Sodium-N-[8-(2-hydroxybenzoyl) amino] caprylate)
 - **Carrier molecule that enhances absorption**
 - Forms weak noncovalent bonds with oral semaglutide
 - Local buffering effect: Prevents breakdown by gastric enzymes and stomach acid
 - **Locally absorbed in the stomach near the site of tablet erosion**
 - Once absorbed, the weak bonds break and SNAC is rapidly eliminated by the kidneys with an average T_{1/2} of 1.3 hrs for SNAC.
- **Once in the blood stream oral semaglutide binds to albumin in the bloodstream resulting in a long half-life (168 hours)**
- Considered safe in patients with eGFR: 30-59 ml/min per CKD-EPI

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Oral Semaglutide – Rybelsus

Important Administration Instructions:

- Instruct patients **to take oral semaglutide at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water only. Waiting less than 30 minutes, or taking oral semaglutide with food, beverages (other than plain water) or other oral medications will lessen the effect of oral semaglutide by decreasing its absorption. Waiting more than 30 minutes to eat may increase the absorption of oral semaglutide.**
 - The estimated absolute bioavailability of semaglutide is approximately 0.4%-1%, following oral administration as recommended.
- Swallow tablets whole. Do not split, crush, or chew tablets.
- Recommended Dosage: **Start oral semaglutide with 3 mg once daily for 30 days. The 3 mg dose is intended for treatment initiation and is not effective for glycemic control. After 30 days on the 3 mg dose, increase the dose to 7 mg once daily. Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose.**

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Phase 3 Clinical Trials

PIONEER 1		• Monotherapy
PIONEER 2		• Oral semaglutide vs. empagliflozin
PIONEER 3		• Oral semaglutide vs. sitagliptin (long-term)
PIONEER 4		• Oral semaglutide vs. liraglutide
PIONEER 5		• Patients with moderate renal impairment
PIONEER 6		• Cardiovascular outcomes
PIONEER 7		• Flexible dose escalation
PIONEER 8		• Oral semaglutide as an insulin add-on
PIONEER 9		• JAPAN monotherapy
PIONEER 10		• JAPAN OAD combination

Novo Nordisk. Capital Market Days, 2017.

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Oral Semaglutide – Rybelsus

- **2-22-2018 PIONEER 1** was a 26-week, randomized, double-blinded, placebo-controlled, four-armed, parallel-group, multicenter, multinational trial comparing the efficacy and safety of three dose levels of once-daily oral semaglutide vs placebo in people with type 2 diabetes treated with diet and exercise only. **703 people** were enrolled in PIONEER 1 and randomized 1:1:1:1 to receive either a **dose of oral semaglutide (3, 7 or 14 mg) or placebo once daily**. The primary endpoint was change in HbA_{1c} from baseline at week 26.
- Patients treated with 3, 7 and 14 mg oral semaglutide achieved **reductions in HbA_{1c} of 0.8%, 1.3% and 1.5%, respectively, compared to a reduction of 0.1% in people treated with placebo from a mean baseline of 8.0%**.
- Patients treated with 3, 7 and 14 mg oral semaglutide experienced a **weight loss of 1.7 kg, 2.5 kg and 4.1 kg, respectively, compared to a weight loss of 1.5 kg in people treated with placebo**. (mean baseline body weight of 88 kg and a BMI of 31.8 kg/m²)
 - The most common adverse event for all three oral semaglutide doses was **mild to moderate nausea(5-16% vs. 6% placebo), which diminished over time**.

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Oral Semaglutide – Rybelsus

- **Oral Semaglutide vs. Empagliflozin Added On to Metformin Monotherapy in Uncontrolled Type 2 Diabetes: PIONEER 2**
- **oral semaglutide (sema) 14 mg once daily (N=411) was compared with the SGLT2i empagliflozin (empa) 25 mg QD (N=410) in patients (pts) with T2D uncontrolled on metformin in a 52-week randomized, open-label trial**
- Proportions of adverse events (AEs) were similar between oral sema (70.5%) and empa (69.2%). The most frequent AEs with oral sema were mild/moderate gastrointestinal events. **Premature trial product discontinuations due to AEs were 11% (oral sema) vs. 4% (empa)**.

Diabetes 2019 Jun; 68(Supplement 1): -.
<https://doi.org/10.2337/db19-54-OR>

Key baseline characteristics	Oral sema 14 mg (N=411)	Empa 25 mg (N=410)		
Male, %	50.1	51.0		
Age, years (SD)	57 (10)	58 (10)		
Diabetes duration, years (SD)	7.2 (5.8)	7.7 (6.3)		
HbA _{1c} , % (SD)	8.1 (0.9)	8.1 (0.9)		
Body weight, kg (SD)	91.9 (20.5)	91.3 (20.1)		
Endpoints by week and estimand	Treatment policy estimand		Trial product estimand	
	Oral sema 14 mg	Empa 25 mg	Oral sema 14 mg	Empa 25 mg
Estimated change from baseline in HbA_{1c}, %-points (primary endpoint)				
Week 26	-1.3	-0.9	-1.4	-0.9
ETD [95% CI]	-0.4 [-0.6, -0.3]***		-0.5 [-0.7, -0.4]***	
Week 52	-1.3	-0.9	-1.3	-0.8
ETD [95% CI]	-0.4 [-0.5, -0.3]***		-0.5 [-0.7, -0.4]***	
Estimated change from baseline in body weight, kg (confirmatory secondary endpoint)				
Week 26	-3.8	-3.7	-4.2	-3.8
ETD [95% CI]	-0.1 [-0.7, 0.5]		-0.4 [-1.0, 0.1]	
Week 52	-3.8	-3.6	-4.7	-3.8
ETD [95% CI]	-0.2 [-0.9, 0.5]		-0.9 [-1.6, -0.2]*	
Observed proportion with HbA_{1c} <7.0%, % of patients				
Week 26	66.8	40.0	70.3	40.7
EOR [95% CI]	3.39 [2.47, 4.65]***		4.08 [2.92, 5.70]***	
Week 52	66.1	43.2	71.6	47.5
EOR [95% CI]	2.71 [1.99, 3.69]***		3.15 [2.25, 4.40]***	

Baseline data are means unless specified otherwise. Changes and treatment differences are estimated means; proportions are observed. Treatment policy estimand: Data collected irrespective of discontinuation of trial product or initiation of rescue medication were included. Trial product estimand: Data collected after discontinuation of trial product or initiation of rescue medication were excluded. Hypotheses related to the treatment policy estimand with primary and confirmatory secondary endpoints (both assessed at week 26) were controlled for multiplicity. P-values are unadjusted two-sided p-values for the test of no difference, *p<0.05, ***p<0.0001 vs empa.

CI, confidence interval; empa, empagliflozin; EOR, estimated odds ratio; ETD, estimated treatment difference; sema, semaglutide; SD, standard deviation.

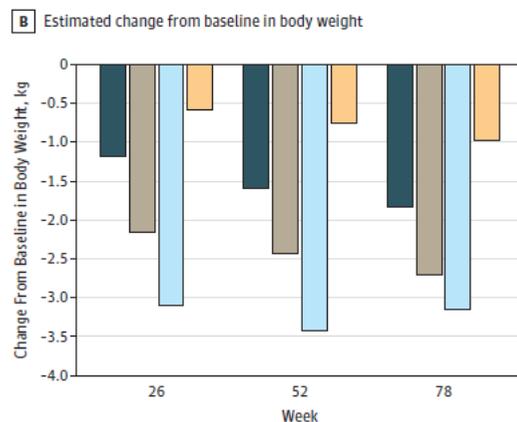
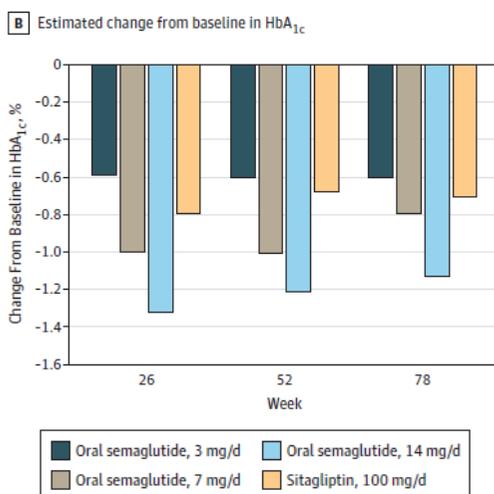
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Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea - The PIONEER 3 Randomized Clinical Trial

- **1864 adults with type 2 diabetes uncontrolled with metformin with or without sulfonylurea were randomized to receive once-daily oral semaglutide, 3 mg (n = 466), 7 mg (n = 466), or 14 mg (n = 465), or sitagliptin, 100 mg (n = 467).** Semaglutide was initiated at 3 mg/d and escalated every 4 weeks, first to 7 mg/d then to 14 mg/d, until the randomized dosage was achieved.
 - (mean age, 58 [SD, 10] years; mean baseline HbA_{1c}, 8.3% [SD, 0.9%]; mean body mass index, 32.5 [SD, 6.4]; n=879 [47.2%] women), 1758 (94.3%) completed the trial and 298 prematurely discontinued treatment (16.7% for semaglutide, 3 mg/d; 15.0% for semaglutide, 7 mg/d; 19.1% for semaglutide, 14 mg/d; and 13.1% for sitagliptin).
 - JAMA. 2019;321(15):1466-1480

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Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea The PIONEER 3 Randomized Clinical Trial



JAMA. 2019;321(15):1466-1480

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Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea - The PIONEER 3 Randomized Clinical Trial

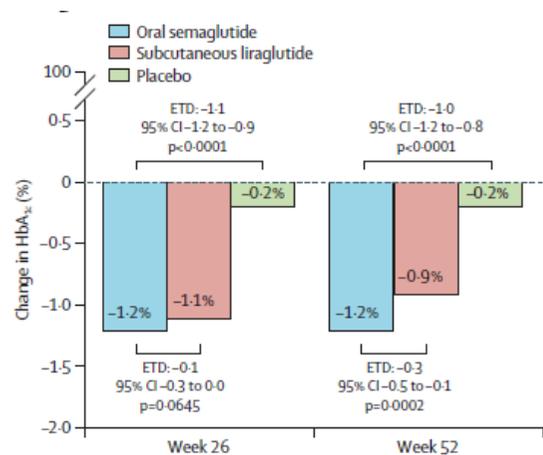
- **Symptomatic hypoglycemia were experienced by 4.9% (23/466), 5.2% (24/464), and 7.7% (36/465) of patients in the 3-, 7-, and 14-mg/d semaglutide groups, respectively, and by 8.4% (39/466) in the sitagliptin group.** (These episodes mainly occurred in patients prescribed background metformin with sulfonylurea).
- **Adverse events led to premature discontinuation for 5.6% (26/466), 5.8% (27/464), and 11.6% (54/465) in the 3-, 7-, and 14-mg/d semaglutide groups, respectively, and 5.2% (24/466) for sitagliptin, with gastrointestinal adverse events being the primary cause in all treatment groups.** (For a substantial proportion of patients in the 7- and 14-mg/d semaglutide groups who discontinued because of an adverse event, the onset of the causative event occurred during the dosage-escalation period).

JAMA. 2019;321(15):1466-1480

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Oral Semaglutide – Rybelsus

- **Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4):** a randomized, double-blind, phase 3a trial
- 711 patients were randomly assigned to oral semaglutide (n=285), subcutaneous liraglutide (n=284), or placebo (n=142). 341 (48%) were female and the mean age was 56 years
- weight loss at week 26 was significantly greater with oral semaglutide than with subcutaneous liraglutide (–1.5 kg, 95% CI –2.2 to –0.9; p<0.0001) and placebo (ETD –4.0 kg, –4.8 to –3.2; p<0.0001).
- Adverse events were more frequent with oral semaglutide (n=229 [80%]) and subcutaneous liraglutide (n=211 [74%]) than with placebo (n=95 [67%]).



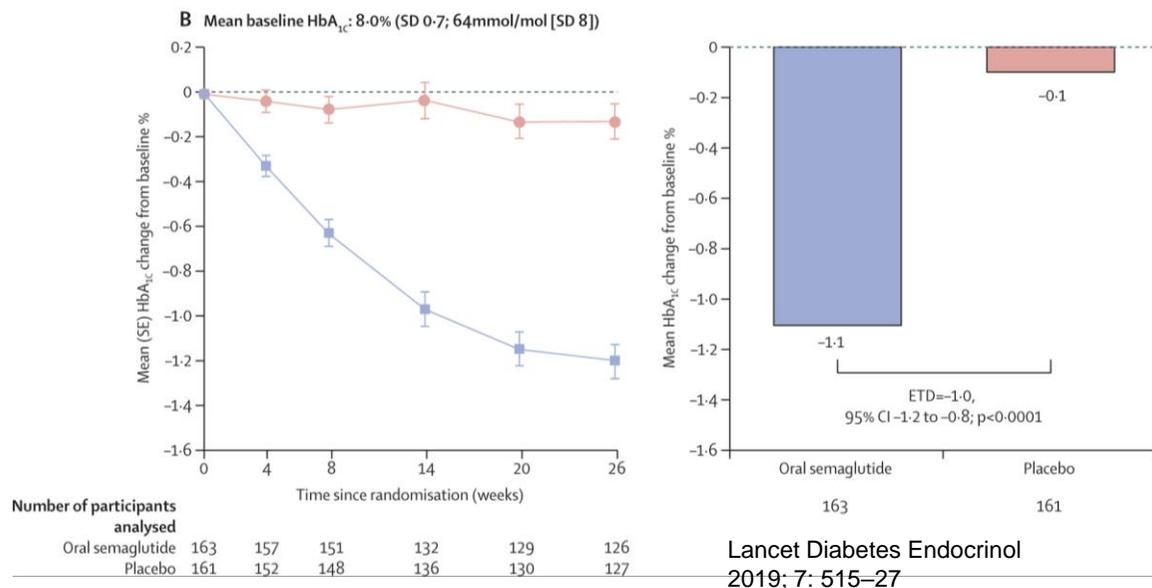
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Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5)

- Patients were aged 18 years or older, with type 2 diabetes (diagnosed ≥ 90 days before screening), had a **HbA_{1c} of 7.0–9.5% and moderate renal impairment** (Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] stage 3), **defined as an eGFR of 30–59 mL/min per 1.73 m², 324 patients were randomly assigned (1:1) to receive either once-daily oral semaglutide (escalated to 14 mg) or placebo, in addition to their background medication (metformin, sulfonylureas, both or basal insulin with or without metformin) and followed for 26 weeks.**
- **Endpoints were change from baseline to week 26 in HbA_{1c} (primary endpoint) and bodyweight (confirmatory secondary endpoint), assessed in all participants with sufficient data.**
 - Lancet Diabetes Endocrinol 2019; 7: 515–27

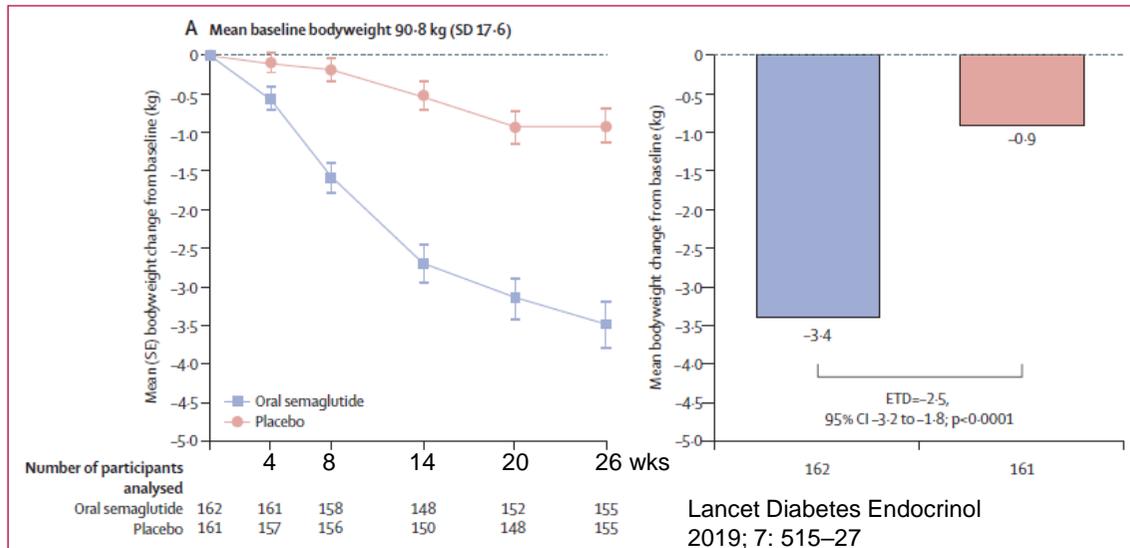
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Oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5)



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Oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5)



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Oral Semaglutide – Rybelsus

- **PIONEER 6 Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (NEJM 2019; 381:841-851)**
 - **3,183 patients (median age 66 years, 68% male) with type 2 diabetes at high cardiovascular risk having standard-of-care treatment were randomized to oral semaglutide (target dose 14 mg) once daily vs. placebo**
 - patients ≥ 50 years old had established cardiovascular disease or chronic kidney disease; patients ≥ 60 years old had cardiovascular risk factors only
 - patients were taking metformin (77%), insulin (61%), sulfonylureas (32%), sodium-glucose cotransporter 2 inhibitors (9.6%), antihypertensive medication (94%), lipid-lowering medication (85%) and antiplatelet or antithrombotic medication (79%)
 - **major adverse cardiovascular event (3 point MACE) defined as cardiovascular death (including death from undetermined causes), nonfatal myocardial infarction, or nonfatal stroke** N Engl J Med 2019;381:841-851

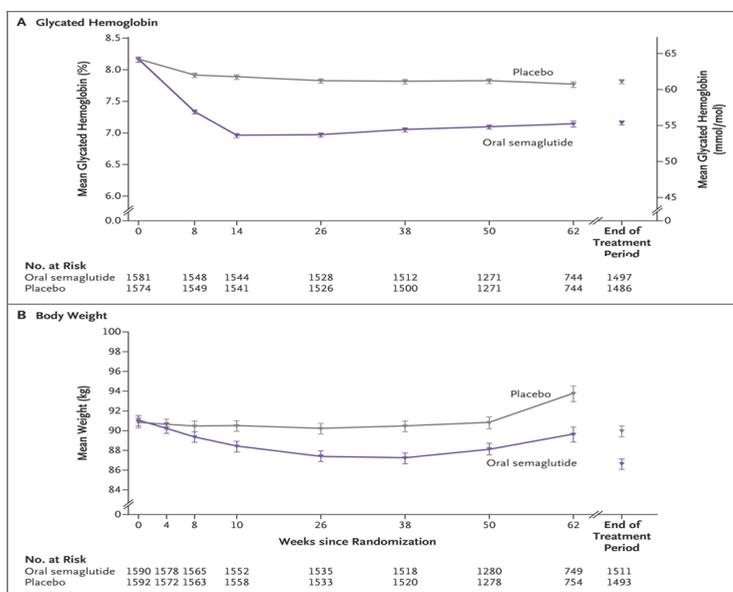
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Oral Semaglutide – Rybelsus

- Results comparing oral semaglutide vs. placebo in intention-to-treat analysis (**median follow-up 15.9 months**)
- **3 Point MACE in 3.8% vs. 4.8% (hazard ratio 0.79, 95% CI 0.57-1.11, noninferiority met, $p=0.17$ for superiority N.S.)**
 - **Cardiovascular death in 0.9% vs. 1.9% ($p < 0.05$, NNT 100)**
 - Nonfatal myocardial infarction in 2.3% vs. 1.9% (not significant)
 - Nonfatal stroke in 0.8% vs. 1% (not significant)
 - **All-cause death in 1.4% vs. 2.8% ($p < 0.05$, NNT 72)**
 - Unstable angina resulting in hospitalization in 0.7% vs. 0.4% (not significant)
 - Heart failure resulting in hospitalization in 1% vs. 1.5% (not significant)
 - N Engl J Med 2019;381:841-851

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Oral Semaglutide – Rybelsus



Glycated hemoglobin levels decreased more in the oral semaglutide group than in the placebo group (mean change from baseline to end of trial, -1.0 vs. -0.3 percentage points), as did body weight (mean change from baseline to end of trial, -4.2 kg vs. -0.8 kg)

N Engl J Med 2019;381:841-851

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Oral Semaglutide – Rybelsus

Adverse Events:

- **Discontinuation due to adverse event in 11.6% vs. 6.5%**
- Any serious adverse event in 18.9% vs. 22.5%
- Acute kidney injury in 2% vs. 2.3%
- Acute pancreatitis in 0.1% vs. 0.2%
- **Retinopathy or related complication in 7.1% vs. 6.3%**
- **Severe hypoglycemia in 1.4% vs. 0.8%**
- Malignant neoplasm in 2.6% vs. 3%
 - N Engl J Med 2019;381:841-851

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Oral Semaglutide – Rybelsus

Table 1. Adverse Reactions in Placebo-Controlled Trials Reported in $\geq 5\%$ of RYBELSUS-Treated Patients with Type 2 Diabetes Mellitus

Adverse Reaction	Placebo (N=362) %	RYBELSUS® 7 mg (N=356) %	RYBELSUS® 14 mg (N=356) %
Nausea	6	11	20
Abdominal Pain	4	10	11
Diarrhea	4	9	10
Decreased appetite	1	6	9
Vomiting	3	6	8
Constipation	2	6	5

In the pool of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1.

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Oral Semaglutide – Rybelsus

Drug Interactions:

- Semaglutide causes a delay of gastric emptying, and thereby has the potential to impact the absorption of other oral medications.
- Levothyroxine exposure was increased 33% (90% CI: 125-142) when administered with oral semaglutide in a drug interaction study.

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Oral Semaglutide – Rybelsus

Immunogenicity:

- Across the placebo- and active-controlled glycemic control trials with antibody measurements, 14 (0.5%) oral semaglutide-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in semaglutide.
- Of the 14 semaglutide-treated patients that developed semaglutide ADAs, 7 patients (0.2% of the overall population) developed antibodies cross-reacting with native GLP-1. The neutralizing activity of the antibodies is uncertain at this time.

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