Experiential Learning Experience Activity – Hyperlipidemia (KEY)

This document is a suggested learning activity for pharmacy learners (APPE, PGY1, PGY2 residents) to complete during their ambulatory care rotation block. Consider using as a pre-test/post-test or as a topic discussion with preceptor.

Optional Recommended Reading:

- 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guidelines on Management of Blood Cholesterol: https://www.ahajournals.org/doi/10.1161/cir.0000000000000625
- Dureden M et al. Cardiovascular risk assessment and lipid modification: NICE guidelines. 2015: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4484941/
- Wilkins J, Lloyd-Jones DM. Novel lipid-lowering therapies to reduce cardiovascular risk. JAMA. 2021;326(3):266-67. https://jamanetwork.com/journals/jama/fullarticle/2782198?utm_source=podcast_platforms&utm_medium=referral&utm_campaign=related_article_links

Overview:

1. Explain the pathophysiology of hyperlipidemia related to increased cardiovascular risk. **As lipids increase within the body, they can lead to deposits on the walls of the arteries. This poses two risks; narrowing of the arteries leading to decreased blood flow, or the deposit can break off and embolize. Either of these may lead to ASCVD.**

2. Define the four benefit categories specified in the 2018 AHA/ACC Cholesterol guidelines. What is the goal LDL lowering for each?

Benefit Category Population	LDL Goal
Clinical ASCVD*	< 70 mg/dL
Severe hypercholesterolemia (LDL ≥190 mg/dL)	< 100 mg/dL
Age 40-75 years + diabetes mellitus	≥ 50% decrease**
Age 40-75 + LDL between 70-189 mg/dL	≥ 50% decrease**

*Clinical ASCVD=ACS (history of MI, stable/unstable angina, coronary or other revascularization, stroke, TIA, or PAD)
**Depending on statin intensity chosen

3. Non-statin therapy:
   a. What other drug classes are included in the guidelines?
      LDL-lowering therapies:
      - **Cholesterol absorption inhibitors (ezetimibe)**
      - **PCSK9 inhibitors**
      - **Bile acid sequestrants**

      Triglyceride-lowering therapies:
      - **Niacin**
      - **Fibrates**

- **Fish oils**

b. When do you use them?
Ezetimibe & PCSK9 inhibitors:
- **Initiate as add-on treatment to maximally-tolerated statin therapy if LDL remains above goal (≥70 mg/dL or ≥100 mg/dL, depending on category patient falls into)**
- **Initiate in patients who are unable to tolerate statin therapy**

Bile acid sequestrants:
- **Initiate in patients who are unable to tolerate statin therapy**

Triglyceride-lowering therapies:
- **Initiate as add-on treatment to maximally-tolerated statin therapy if TGs remain elevated (≥500 mg/dL)**

c. Do any have cardiovascular benefit – if so, which ones?
Ezetimibe
PCSK9 inhibitors
Vascepa

4. Please complete the following graph in terms of percentage increase, decrease or no change for each medication/medication class.

	LDL	HDL	Triglycerides
Statins	↓20-55%	↑5-15%	↓10-30%
Ezetimibe	↓13-20%	↑1-3%	↓5-10%
Niacin	↓5-25%	↑15-35%	↓20-50%
Fenofibrate	↓5-20%*	↑15%	↓20-50%
Lovaza©	↑44%	↑9%	↓45%
Bempedoic acid	↓18-24%	-	-
Vascepa©	-	↑9%	↓45%
Inclisiran	↓52%	↑6%	↓7%

*Can increase LDL when TGs are high

5. Please list the available high intensity statins (names/strengths).
- **Atorvastatin 40-80mg**
- **Rosuvastatin 20-40mg**

6. One of the most common side effects/concerns with statin therapy is myopathy. If myalgias occur with statin use name three strategies to minimize this side effect yet keep the patient on statin therapy. Be specific.
1. **Hold statin. After 2-4 weeks, re-challenge with same statin at same dose.**
2. **Hold statin. After 2-4 weeks, re-challenge with lower dose of same statin.**
3. **Hold statin. After 2-4 weeks, re-challenge with different statin with lower myopathy risk (ex: pravastatin, rosuvastatin).**
4. **Hold statin. After 2-4 weeks, re-challenge with statin therapy and co-enzyme Q10**

5. **Hold statin. After 2-4 weeks, re-challenge with every other day statin (ex: MWF)**

7. What statin(s) are preferred in renal dysfunction?
   Atorvastatin

8. When does a statin need to be discontinued based on liver function/CK values? Can a statin be tried again in each circumstance?
   Liver function tests: > 3x ULN; can retry once normalized
   CK: 10x ULN; AACE notes not to retrial if due rhabdomyolysis

9. What is the relationship between vitamin D levels and statin intolerance?
   Low vitamin D levels are correlated to higher incidence of myopathy from statins.
   a. Example vitamin D dosing strategy:**Ergocalciferol (D2) & cholecalciferol (D3):**
      - **25(OH)D level < 12 ng/mL: 50,000 units once weekly for 6-12 weeks**
      - **25(OH)D level 12 - < 20 ng/mL: 800-1000 units once daily for 3-4 months**

10. What herbal supplement is available that has a statin as a primary ingredient?
    Red yeast rice

11. Please discuss the drug-drug interaction with gemfibrozil and statin therapy. What would you do if a patient was prescribed simvastatin and gemfibrozil (statin is indicated AND prior history of TG >500)?
    Statins utilize the OATP1B1 transporter within hepatocytes in order to be removed from the body. Gemfibrozil inhibits OATP1B1, reducing the elimination of statins from the body, therefore increasing the risk of statin-induced myopathy. Furthermore, simvastatin is metabolized by CYP2C8, which is also inhibited by gemfibrozil, leading to increased simvastatin levels. This is why gemfibrozil is contraindicated with simvastatin.
    If a patient were prescribed simvastatin and gemfibrozil, it would be appropriate to switch the patient from gemfibrozil (which ultimately should not be used with statins) to Vascepa, which also lowers TGs without increasing the risk of myopathies from statins. Fenofibrate may also be appropriate, but may increase the risk of myopathy.

12. PCSK9 inhibitors and Inclisiran:
    a. Explain the mechanism of action of both:
       PCSK9 inhibitors: PCSK9 is an enzyme responsible for decreasing LDL receptors. These receptors gather circulating LDL, leading to decreases in LDL levels. By inhibiting the PCSK9 enzyme, LDL receptors increase, leading to decreased LDL levels.
       Inclisiran: Decreases PCSK9 enzyme levels, leading to increases in LDL receptors and therefore decreases LDL levels.

    b. How are the medications administered; please counsel a patient on their use:
       Both classes are administered subcutaneously into the abdomen, upper arm, or thigh. Inclisiran is administered every 6 months, while Praluent® and

Repatha® are every 2-4 weeks depending on the strength. Inclisiran must be administered by a health care professional. The most common side effects of both classes are injection site reactions. Inclisiran may also cause arthralgia, UTI, diarrhea, bronchitis, pain in extremities, and dyspnea. Repatha® and Praluent® may can nasopharyngitis, influenza, upper respiratory tract infections (URTIs), and urinary tract infections (UTIs). Additionally, Repatha® may cause back pain, while Praluent® can increase LFTs. Inclisiran is stored at room temperature, while Praluent® and Repatha® should be stored in the refrigerator and allowed to warm to room temperature before administration. Repatha® and Praluent® may be stored at room temperature for 30 days.

13. What is the literature for the following agents and potential mortality benefits?
    a. Repatha®
        i. **FOURIER Trial (2017): Repatha® at a dose of 140mg every two weeks or 420mg monthly in addition to statin therapy significantly lowered the risk of cardiovascular events and death when compared to placebo.**
    b. Inclisiran
        i. **ORION-10 and ORION-11 Trials (2020): Inclisiran significantly lowered LDL levels compared to placebo (~50%decrease). There are currently no clinical trials demonstrating effects on cardiovascular morbidity or morality. As of 2022, the trial is currently ongoing for CV benefit.**
    c. Vascepa®
        i. **REDUCE-IT Trial (2019): Vascepa® at a dose of 2 grams twice daily in addition to statin therapy significantly lowered the risk of cardiovascular events and death when compared to placebo.**

14. For patients with established cardiovascular disease who need further triglyceride lowering after the addition of a statin, which medication would be preferred and why?
    Vascepa (icosapent ethyl) would be preferred due to its cardiovascular benefit.

Test Prep Questions:

15. A 76yo man with PMH of HTN x 15 yrs, ventricular tachycardia x 5 yrs, and ischemic heart disease with MI 3 years ago has the following FLP: LDL 110, HDL 28, and TRG 80. Current meds are ASA 81mg/d, Plavix 75mg/d, amiodarone 400mg/d, carvedilol 25mg BID, lisinopril 40mg/d and simvastatin 20mg/d. Which of the following changes should be made to help this patient reach his LDL goal?
    a. Increase simvastatin to 40mg/d **– simvastatin 20-40mg are both moderate intensity**
    b. Increase simvastatin to 80mg/d **– should never initiate simvastatin 80mg due to increased risk of myalgias**
    c. Change simvastatin to atorvastatin 80mg/d
    d. He is at goal and does not need any changes **– goal LDL < 70 mg/dL**

This patient is on statin therapy for secondary prevention, making his LDL goal < 70 mg/dL. Because he is not at this goal with his current regimen of simvastatin 20mg, he should be switched to a high-intensity statin. Caution is advised due to the patient's age being >75 years. Closely monitor and follow-up with the increasing the intensity of his statin.

16. At what point are fibric acids indicated for hypertriglyceridemia per the AHA/ACC guidelines?
    a. 150 mg/dl
    b. 250 mg/dl
    c. 350 mg/dl
    d. 450 mg/dl
    e. 500 mg/dl – **due to the risk of pancreatitis**

17. JM is a 64-year-old woman with a PMH of pancreatitis (when TG 2200 mg/dL), uncontrolled gout, severe psoriasis, recurrent infections requiring hospitalization, and lovastatin-associated myopathy. Her current medications include rosuvastatin, prednisone, and allopurinol. Colchicine was also added a few days ago for a gout exacerbation. She reports an anaphylactic reaction after eating seafood in college. Her LDL-C is 96 mg/dL, HDL-C 42 mg/dL, and TG 640 mg/dL. Which of the following is the safest addition to her therapy?
    a. Niacin **- ↑ uric acid**
    b. Colesevelam **– can increase TGs, avoid if TGs > 300 mg/dL**
    c. Fish oil **– seafood anaphylactic allergy**
    d. Fenofibrate

18. Which patient would qualify for a high intensity statin?
    a. An 72 yo male being discharged from the ED due to stroke **– this patient falls into secondary prevention group due to having a stroke/clinical ASCVD**
    b. A 53 yo female with diabetes, LDL of 165 and ASCVD risk score of 6.3% **- Diabetes diagnosis prompts treatment with either a high or moderate-intensity statin. Her ASCVD risk score is low, so a moderate-intensity statin would be more appropriate.**
    c. A 45 yo with a ASCVD risk score of 6.8% **- this patient would likely not need statin therapy, depending on LDL levels and other risk-enhancing factors.**
    d. A 58 yo with an LDL of 170 **– would need to assess ASCVD risk to determine appropriate intensity (≥20%= high intensity, 7.5-19.5%= moderate intensity)**

19. Which of these statins has the lowest risk for myopathy/myalgia and why?
    a. Lipitor; high protein binding
    b. Zocor; CYP3A4 substrate
    c. Livalo; rapid absorption
    d. Crestor; high hydrophilicity

20. A 65-year-old male with a past medical history significant for hypertension, peripheral artery disease and type 2 diabetes is being seen for a follow-up visit today at his PCP's office. One month ago, he was diagnosed with hyperlipidemia was prescribed atorvastatin 40mg to lower his lipid levels as well as for cardiovascular protection. He

reports tolerating the medication well with no adverse effects. At his appointment today, his most recent lab work is as follows:

LDL: 70 mg/dL
HDL: 45 mg/dL
Triglycerides: 502 mg/dL

Which medication is appropriate to initiate today?

a) Ezetimibe **– usually used for add-on treatment with maximally-tolerated statin therapy to further lower LDL. Patient's LDL is below goal, but TGs are elevated.**
b) Colesevelam **– usually used to lower LDL if statins are not tolerated. Can increase TGs**
c) Vascepa **– patient has no contraindications to fish oils and Vascepa has CV benefit, making it a better choice than fenofibrate in this case**
d) Fenofibrate **– may be appropriate, but may increase risk of statin-induced myopathy**

Patient Cases:

1. A 56 year old white male comes to your office. Vitals show BP 140/94, P 80, RR 18 and labs show BMP WNL but FLP shows TC 240, LDL 150, HDL 20 and TG 150. In addition, you smell cigarette smoke on him, which you ask about. He replies that you are correct and he should really stop since both his parents died of MIs in their 50's.
   a) Which group does he belong and what is your plan?
      This patient belongs in the primary prevention category with patients age 40-75 and LDL between 70-189 mg/dL. His calculated 10-year ASCVD risk is high at around ~31%. The plan for lipid-lowering therapy should be to initiate a high-intensity statin and he should also be offered smoking cessation therapy if interested.
   b) What is your goal? When would you recheck to see if you attain this goal?
      The goal with high-intensity statins is to lower LDL by at least 50%. A lipid panel should be performed in 4-12 weeks to assess the effects of therapy on total cholesterol, LDL, HDL, and TGs.

2. A 61 yom with PMH significant for HTN, depression, CAD with unstable angina, HFrEF, OSA, and GERD presents for an annual appointment and follow up. Current medications include: aspirin 81 mg daily, carvedilol 6.25 mg BID, nitroglycerin 0.3 mg SL PRN, omeprazole 20 mg BID, sertraline 50 mg daily.

Calcium				9.2			9.0
Ionized Calcium							1.21
Normalized CAlcium							1.25
Magnesium				1.6			
Phosphorus							2.6
Albumin				3.2			
Bilirubin, Total				1.0			
Alkaline Phosphatase				93			
ALT				17			
AST				24			
Anion Gap				15			10
NT Pro BNP				3,911			
eGFR-African American				>60			>60
eGFR-All Other Races				>60 *			>60 *
eGFR							
Vitamin B12	467						
Folate							
Ferritin							337.9
Iron							
TIBC							
Transferrin Satura...							
CRP							19.1
Cholesterol, Total	269 *						
Triglyceride	239 *						
Fasting Time	12						
HDL Cholesterol	35 *						
LDL Cholesterol	186 *						
VLDL Cholesterol	48						
TC:HDL Ratio	7.69						
LDL:HDL Ratio	5.31 *						
Non HDL Cholesterol	234 *						
Vitamin D 25 Hydroxy	23.8 *						

a) What is this patient's goal LDL?

This patient has ASCVD (CAD with unstable angina), so his goal LDL would be < 70 mg/dL.

b) What would you recommend for this patient's HLD care? Be specific on dose, regimen.

Atorvastatin 40mg-80mg PO once daily or rosuvastatin 20-40 mg PO once daily – follow up lipid panel in 4-12 weeks

c) Please provide key counseling points.

Avoid grapefruit/grapefruit juice
Muscle pain is a common side effect – report this to your provider
Because rosuvastatin and atorvastatin are longer acting, do not need to take in the evening like other statins

Over a period of 6 months, you increase the medication you initiated to maximum dose. The patient is tolerating well without issues. Resulting cholesterol panel collected today is: total cholesterol 135, LDL 84, TG 121

a) What changes, if any, would you make at this time?

If patient was started on atorvastatin 40 mg daily or rosuvastatin 20 mg daily – increase to max dose. If started on max dose yet not at his LDL goal, an additional agent should be added on. Ezetimibe or PSCK9 inhibitors are the preferred add on agents to further lower LDL. Due to how costly PSCK9 inhibitors are, ezetimibe 10mg PO daily should be initiated.

3. A 47 yo AAf presents for follow up to your family medicine clinic for diabetes. Other PMH include: HTN, asthma, back pain, and depression. Current medications include: albuterol – 1 puff Q6H PRN, budesonide/formoterol 2 puffs BID, cetirizine 10 mg daily, metformin 1,000 mg BID, escitalopram 20 mg daily, and losartan 100 mg daily. Patient is a non-smoker. Last BP – 124/57, weight 201 lbs, height 5'4". BMP WNL, HbA1c today 6.7%; total cholesterol 155, TG 112, HDL 48, LDL 85. What is this patient's indication for statin therapy? Please describe the plan for this patient's HLD.

   This patient's indication for statin therapy is his diagnosis of diabetes, so either a high or moderate-intensity statin should be initiated. To decide between which intensity to initiate, ASCVD risk factors must be considered. The patient's only risk factor is her ethnicity, so it is reasonable to initiate a moderate-intensity statin, such as atorvastatin 20mg PO daily. In 4-12 weeks, a lipid panel should be performed to assess the statin's effects on her total cholesterol, LDL, HDL, and TGs. With a moderate-intensity statin, we would expect a 30-49%decrease in LDL. The patient should also be monitored for side effects such as myalgia from statin therapy.