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Statin Use in Pregnancy: A Clinician Update

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During gestation, maternal lipid production is increased in response to fetal needs. Triglyceride levels markedly rise two to four times pre-pregnancy levels by the third trimester and decline rapidly post-delivery.[1] Pregnancy also alters the composition of low-density lipoprotein (LDL) particles, resulting in smaller, denser particles more susceptible to atherogenesis. High-density lipoprotein (HDL) levels also proportionally rise with other lipid levels in response to pregnancy. Cholesterol synthesis is a foundational step in fetal development leading to the synthesis of steroids and fetal cell membranes. Therefore, decreasing cholesterol synthesis could cause fetal harm,[2] however, rapid increases in lipid levels can increase chances of maternal cardiovascular disease during pregnancy and post-partum. Cardiovascular disease accounts for 26.5% of deaths during pregnancy.[3] In addition, approximately 1 in 500 people are affected by familial hypercholesterolemia and of those individuals, pregnant women are at high risk considering the limitation in treatment options.[2] Primary treatment can prevent up to 68% of cardiovascular related deaths in pregnancy.[4] Maternal hyperlipidemia also poses threat to the fetus which could result in pre-term delivery.[5] Cardiovascular risk has increased in pregnant patients recently due to an increase in maternal obesity, delayed pregnancy, and increasing maternal age.[5]

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A prior trial conducted by Lankas et al. found fetal developmental toxicity/teratogenicity induced by exceedingly high lovastatin doses in rats and rabbits.[6] Many biological females of child-bearing age may benefit from statin therapy, however prior to recent pregnancy category updates by the Food and Drug Administration (FDA) in July 2021, statin use during pregnancy was contraindicated. Patient populations that may benefit from statin use include those with preeclampsia, polycystic ovary syndrome, endometriosis, hyperlipidemia, diabetes, and others.[5] Concerning the use of statins in pregnancy, the FDA currently recommends health care professionals to "consider the ongoing therapeutic needs of the individual patient, especially patients at very high risk of cardiovascular events during pregnancy, such as patients with homozygous familial hypercholesterolemia or those with established cardiovascular disease" when evaluating if the use of statin in warrented.[7] With the recent removal of the strict FDA contraindication against statins in pregnancy, patients and providers can make individualized decisions based on patient health for optimal outcomes for both mother and fetus outside of previous first-line recommended agents, including niacin and bile acid sequestrants.

Atherosclerotic cardiovascular disease (ASCVD) risk is defined as the presence of atherosclerotic cardiovascular disease such as: acute coronary syndrome, myocardial infarction, stable or unstable angina, stroke/transient ischemic attack, or peripheral arterial disease in combination with various lipid panel values.[8] Low-density lipoprotein cholesterol (LDL-C) is the guiding factor to determining ASCVD risk and categorization.[8] The first-line therapy for cholesterol and lipid lowering in each of the ASCVD risk populations is statins.[9] Other medications used for cholesterol-lowering include ezetimibe, fibrates, niacin, bile acid sequestrants, PCSK9 inhibitors, and fish oil.

This manuscript aims to address pregnant women and the role of statin use within this special population. Statin therapy has already been proven effective in reducing ASCVD risk in women of child-bearing age; the purpose of this manuscript is to elaborate on the maternal and fetal safety profile for statin use in pregnancy. This manuscript will also address changes in FDA pregnancy categories, review trials which led to changes in statin risk assessment, and review data which established safety profiles for statin use during pregnancy and lactation.

Updated Pregnancy Categories

On June 30, 2015, the FDA implemented a new pregnancy category classification system. Decisions based on medication usage during pregnancy are patient specific and therefore a simple graded classification system was not sufficient. The new FDA Pregnancy and Lactation Labeling Rule (PLLR) requires providers to read and interpret potential fetal risk of medications.[10] The standard pregnancy categories, outlined in **Table 1**, have been discontinued and the PLLR guidelines have been implemented. The PLLR guidelines include three revised categories that summa-

Table 1 | Standard Pregnancy Categories Prior to 2015[12]

Category	Clinical Implications
A	Medication failed to demonstrate fetal risk in first trimester during well controlled studies in pregnant women.
B	Animal studies failed to demonstrate fetal risk. No well controlled studies in pregnant women, and no demonstrated adverse effects on fetus.
C	Animal studies failed to demonstrate adverse effects on fetus, or no well controlled studies in animals or humans.
D	Positive demonstration of fetal risk. Benefits may outweigh risks.
E	Positive demonstration of fetal risk. Risks clearly outweigh any possible benefit.

rizes risk of medications used during pregnancy and lactation, relevant clinical data, and discussions to assist in clinical decision making for pregnant patients.[11] As shown in **Table 2**, the previous categories have been relabeled to include more potentially affected patient populations such as pregnant women, lactating women, and females and males of child-bearing potential. The first category is a risk summary pertaining to systemic absorption based on clinical data is included along with the risk of adverse fetal developmental outcomes. This section of the new PLLR classification is available to assist prescribers with dose adjustments, adverse reactions, and labor and delivery effects.[10] The second category is the "Nursing Mothers" category has been revised into the "Lactation" label of pregnancy warnings. This category includes data pertaining to maternal systemic absorption, drug presence in milk, drug effect on milk production, and drug effect on breast-fed children.[11] A risk-benefit summary with clinical data is included in this category to assist in prescribing medications for the lactating mother. The last category of the PLLR is "Females and Males of Reproductive Potential". This labeling includes information on pregnancy testing, contraception, and drug related infertility.[10] This category for labeling includes pre- and post-conception advisories that can prevent adverse effects of medications on pregnancy outcomes.

With the new PLLR, existing clinical data is used to promote patient specific medication therapy decisions between patient and prescriber. The new labeling provides accurate and consistent descriptions of risk versus benefit via underlying information that can be interpreted for clinical decision making. The more clinical data available leads to improved decision making rather than standardized categorization of risks. The lack of clinical data in certain medications can be assessed as low, moderate, or high risk of developmental abnormalities based on previous animal studies or predictive assessment. Clinicians are still encouraged to use sound clinical judgement when evaluating pregnancy and lactation risks.

Clinical Trials

Lovastatin was the first FDA-approved HMG-CoA reductase inhibitor approved in 1987.[14] The FDA contraindication of statins in pregnancy was based on original preclinical safety assessment of the drug on rats and rabbits showing teratogenicity at exceedingly high doses.[14] The contraindication has been accepted as the standard of care for years, but newer studies challenge the classification based on normal fetal development. The recent removal of contraindication status and evaluations of risk versus benefit in pregnant patients allows freedom to prescribe potentially life-altering medications during pregnancy. The following sections review clinical trials which provide fetal safety data to advocate for statin use in high-risk pregnant patients.

Constantine et al.[15]

A pilot, multicenter, double-blind, randomized controlled trial of women conducted by *Constantine et al* assessed the utility of pravastatin in preventing preeclampsia during high-risk pregnancies.[15] Eligible participants were at least 18 years of age with a current pregnancy status between 12 weeks and 16 weeks gestation and a past medical history of severe preeclampsia in a prior pregnancy that required delivery prior to 34 weeks gestation.[15] A total of 21 subjects were enrolled in the study with 11 patients receiving pravastatin 10mg and 10 receiving placebo (low-dose aspirin, which has off-labeled use for preeclampsia).[15] One patient from the pravastatin group withdrew from the study due to social reasons while 10 participants from each group completed the study. No study participants were lost to follow up and patient medication adherence was similar in both groups.[15] All baseline patient characteristics, age, body mass index, blood pressure, and parity were similar between groups.[15]

The primary outcomes of the study were maternal-fetal safety and steady-state levels of pravastatin during versus weeks of pregnancy gestation.[15] Maternal-fetal safety was evaluated by medication side effects, maternal and fetal adverse effects, congenital malformations, and death. Secondary outcomes of the study included rates of preeclampsia and preterm delivery, gestational age at delivery, infant birthweight, and maternal and cord blood lipid profile.[15]

Table 2 | Comparison of Pregnancy and Lactation Labeling Rules: 1979 versus 2015[10]

Rule in Phase-Out	New PLLR
Pregnancy risk letter categories (A, B, C, D, X) assigned.	Pregnancy risk letter categories eliminated.
Section 8.1 Pregnancy Section 8.2 Labor and Delivery	Combined to form one section: 8.1 Pregnancy • Pregnancy Exposure Registry • Risk Summary • Clinical Considerations • Data
Section 8.3 Nursing Mothers	Becomes Section 8.2 Lactation • Risk Summary • Clinical Considerations • Data
Requirement to update the label as information becomes outdated	Requirement to update the label as information becomes outdated
–	New section added: 8.3 Females and Males of Reproductive Potential * • Pregnancy Testing • Contraception • Infertility

PLLR = Pregnancy and Lactation Labeling Rule.

* Only included when there are recommendations or requirements for pregnancy testing and/or contraception before, during, or after drug therapy, and/or there are human and/or animal data suggesting drug-associated effects on fertility and/or preimplantation loss effects.

Results from the trial found no maternal, fetal, or infant deaths or congenital malformations with pravastatin use in either study group.[15] Maternal-fetal safety in the pravastatin group improved with reduced maternal cholesterol concentrations and similar infant birth weight between the trial groups.[15] Statistically significant primary outcomes were observed with an increased half-life of pravastatin within the second and third trimesters, p= 0.02, as well as maternal LDL-C levels during the third trimester statistically decreased with pravastatin use (p=0.02). Fetal total cholesterol concentrations in both the pravastatin and aspirin arms were not statistically significant different. Side effects included musculoskeletal pain, heartburn and headache but were not statistically significant.[15]

Secondary outcomes that were significant included absence of developing preeclampsia with pravastatin use compared to placebo as well as decrease in preterm delivery. There were five preterm deliveries (prior to 37 weeks) in the placebo group, as compared to one in the pravastatin group.[15] After birth, five infants of the placebo group were placed in the NICU compared to two in the pravastatin group. While outcomes may support the use of pravastatin for ASCVD risk reduction in pregnancy, researchers stress further investigation of escalating pravastatin doses during pregnancy and the risk versus benefits support the use of pravastatin 10mg for preeclampsia.[15] The results of the study conclude that maternal cholesterol levels fluctuate independent of fetal cholesterol levels, may provide maternal benefit for stroke prevention, and does not increase risk of cognitive malformations or death for the fetus.[15]

Zarek et al.[5]

A meta-analysis conducted by *Zarek et al.* examining fetal risk and pregnancy outcomes following first trimester exposure to statins was completed in 2014.[5] The meta-analysis included both retrospective and prospective controlled trials, studies of pregnant women exposed to a statin, and studies that included a control group of women not exposed to statins.[5] Six total studies were included in the analysis.

This study found no increased risk of birth defects in the statin-exposed pregnancies as compared to control groups (RR 1.15; 95% CI 0.75 to 1.76).[5] However, there was an increased risk of miscarriage in the statin-exposed pregnancies compared to control groups (RR 1.35; 95% CI 1.04 to 1.75).[5] Results observed are concurrent with no increased risk of teratogenicity with statin use in pregnancy and potential benefits of statin use outweigh risks in certain populations, such as those with endometriosis and preeclampsia.[5] The overall conclusions of the study are consistent with the new FDA recommendation that statins should not contraindicated in pregnancy for use in high-risk indications.

Ofori et al.[2]

This Canadian cohort study conducted by *Ofori et al.* in 2007 aimed to analyze statin exposure groups within defined populations and characterize gestational outcomes. Studied medications included: statins, fibrates, and nicotinic acid; each prescribed at standard recommended therapeutic doses during the first trimester of pregnancy. Researchers created a "Medication and Pregnancy" registry of patients that was assembled into three study groups:

A)women prescribed statins (n=153)
B)women prescribed fibrates/nicotinic acid (n=29)
C)women prescribed statins prior to conception (n=106)

Inclusion criteria for the registry included women of age 15-45 years at the first day of gestation, confirmed insurance for the duration of the study and pregnancy, and have previously been prescribed a statin, fibrate, or nicotinic acid in the year before or during pregnancy.[2] Exclusion from the study included previous use of alternate category X medications such as: carbamazepine, phenytoin, valproic acid, lithium, acitretin, isotretinoin, antineoplastic agents, leflunomide, and androgens.[2] The presence of maternal comorbidities before and during pregnancy was identified as: hypothyroidism, diabetes/gestational diabetes, or chronic hypertension.

The primary outcome of the study focused on determining the relationship between maternal exposure to antilipidemic medications during pregnancy as well as fetal congenital anomalies to live-born infants.[2] The statins included in the trial were: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin at FDA approved doses for ASCVD risk reduction. The fibrates included were: fenofibrate, bezafibrate, and gemfibrozil.[2] Maternal group B was the reference/control group of the study due to the lack of statin therapy to treat hyperlipidemia. Secondary analyses of the groups included variables affecting pregnancy such as maternal age at the end of pregnancy, socioeconomic variables, and comorbidities.

Results from the study found major and minor fetal congenital anomalies as compared to the control which was infants with no documented congenital anomalies within the first 12 months after birth.[2] Mothers (and fetuses) lost to follow up were due to induced abortions or miscarriage/stillbirth/unspecified abortions in each group; trial results were adjusted accordingly.

In study group A, there were 69/153 live births, of which 64 data were collected and there were 3/64 congenital anomalies. There were 14 live births of 15 pregnancies with 3/14 congenital anomalies in group B, the reference group, and 7/67 congenital anomalies in group C.[2] When compared to group B, the odds ratio for congenital anomalies in group A was 0.79 (95% CI 0.10) and the odds ratio for group C was 1.74 (95% CI 0.27).[2] In group A, there were 4.69% of pregnancies with congenital anomalies which is not statistically greater than the 21.43% of anomalies in group B or the 10.45% of anomalies in group C.[2] There were three congenital anomalies of the heart, an unspecified anomaly, ventricular septal defect, and atrial septal defect, identified in group A where the mothers were taking lovastatin, atorvastatin, and simvastatin.[2] Unrelated anomalies in group B: cardiac, musculoskeletal, tuberous sclerosis, and an eye anomaly occured.[2] There were a variety of unrelated congenital anomalies in group C: musculoskeletal, cardiac, and respiratory.[2] To further determine the source of congenital anomalies, by individual statin, all cases of adverse outcomes were analyzed. Outcomes associated with lipophilic statins such as simvastatin, lovastatin, and atorvastatin were associated with greater incidence of congenital anomalies. There were no congenital malformations associated with pravastatin use.[2]

Researchers have concluded the evidence presented in this study provides sufficient data to support that antilipidemic treatment alone is not a probable cause of adverse fetal congenital anomalies.[2] The study also tracked maternal comorbidities during gestation which, without appropriate treatment, can increase the risk of adverse fetal outcomes.[2] The evidence is consistent with the recommendation that statin use during pregnancy is cautioned if unnecessary, but can provide benefit in a need-based population with a limited risk of adverse fetal outcomes.[2]

Clinical Implications

Approximately 35% of women in the United States have cardiovascular disease and is the leading cause of death in women.[16] Cardiovascular disease is present in 1—4% of all pregnancies.[17] Statins are the first-line treatment of cardiovascular disease and without contraindication status are safe to use during pregnancy and may reduce the risk death from cardiovascular disease. The evaluated studies reviewed above provided evidence that statins may not be as teratogenic as once thought and can be safely used during pregnancy for patients with high risk of cardiovascular disease. Due to the ethical components of the topic, large studies have not been performed, and should be done in the future to prove maternal and fetal benefit prior to providing a blanket classification of safe use for a population of child-bearing age.

While this manuscript targets the discussion of statin use in pregnancy, it is relevant to discuss ramifications with this drug classification change on pertinent disease states, such as preeclampsia and gestational diabetes. Preeclampsia previously fell into the contraindicated category of use with statins in pregnancy and could not be treated appropriately. Preeclampsia is a major cause of maternal mortality and affects 2—8% of all pregnancies.[18] Pregnant patients with a history of preeclampsia have a significantly increased chance of future heart failure, stroke, coronary atherosclerosis, and death associated with cardiovascular disease (CVD).[18] Gestational diabetes is directly related to the development of maternal CVD and occurs in approximately 6% of all pregnancies in the United States.[18] The risk of development of CVD is attributed to maternal type 2 diabetes mellitus, which may or may not be caused by gestational diabetes, in which statin therapy is first-line therapy due to increased ASCVD risk.[18] In addition, patients with familial hypercholesterolemia have significantly elevated cholesterol levels pre-pregnancy, which are increased tremendously during pregnancy and increased ASCVD risk during and after pregnancy.[19] Familial hypercholesterolemia has a 10-fold increased risk of heart disease pre-pregnancy, and have an increased risk in developing preeclampsia during pregnancy thus exponentially increasing heart disease risk.[19]

The removal of the contraindication wording of statin use during pregnancy may allows for appropriate therapy for CVD prevention and treatment for these additional disease states. Caution is warranted due to limited trials evaluating long-term effects of statin use during pregnancy and should be prescribed with appropriate and thoughtful clinical judgement.

Conclusion

The FDA removal of contraindication status of statin use in pregnancy may provide therapeutic benefit to an already high-risk patient population. Statin use has previously been proven to reduce risk of adverse cardiovascular events, and now may be used in pregnant patients due to the lack of fetal congenital anomalies found in recent studies. Studies have found that statin therapy during pregnancy proposes equal risk of adverse fetal outcomes to standard antilipidemic treatment during pregnancy with better maternal and fetal outcomes by reducing risk of maternal heart disease during pregnancy and allowing the pregnancy to come full -term. To truly determine the full benefit and risk of statin use during pregnancy, larger prospective trials will need to be conducted. However, with the limited data provided, it appears that statins may be added back into therapy consideration when treating pregnant patients at high-risk for cardiovascular event or disease.

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Personalized Medicine Corner

SLCO1B1 Genotype-Guided Dosing to Reduce Risk of Statin-Associated Myalgias

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The HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors (i.e., statins) are the first-line treatment for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD). Statins are the most commonly prescribed drug class in America. In 2020, atorvastatin, simvastatin, and rosuvastatin were #1, #13, and #17 most commonly prescribed drugs in the U.S., respectively.[1] The hepatic transporter, OATP1B1 (organic anion transporter polypeptide 1B1, also referred to as SLCO1B1), facilitates the hepatic uptake of statins into the liver, where the drugs exert their activity as HMG-CoA reductase (i.e. the enzyme that converts HMG-CoA into mevalonic acid, a cholesterol precursor) inhibitors.[2] The subsequent reduction of cholesterol in hepatocytes lead to an increase in hepatic LDL receptors, which ultimately reduce circulating LDL-cholesterol and its precursors.

OATP1B1-dependent transport is an important step in mediating hepatic clearance of statins. OAT1B1 is encoded by the solute carrier organic anion transporter pharmacogene, *SLCO1B1*.[2] Individuals with decreased or poor SLCO1B1 function (i.e., due to variations in the *SLCO1B1* gene, namely c.521T>C, ...

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….denoted by the *5 variant allele) have reduced transport into hepatocytes, which can markedly increase systemic exposure of statins, and consequently, lead to increased risk of statin-associated musculoskeletal symptoms (SAMS).[3] SAMS include a range of clinical manifestations from myalgia to myopathy, and rarely rhabdomyolysis.

Interpretation of Pharmacogenetic Results

Individuals with two normal function alleles (*SLCO1B1*1/*1*) have a SLCO1B1 normal function phenotype, while individuals with one normal function allele and one no function variant allele (e.g., *SLCO1B1*1/*5*) have a SLCO1B1 decreased function phenotype and individuals with two no function alleles (e.g., *SLCO1B1*5/*5*) have a SLCO1B1 poor function phenotype.[3]

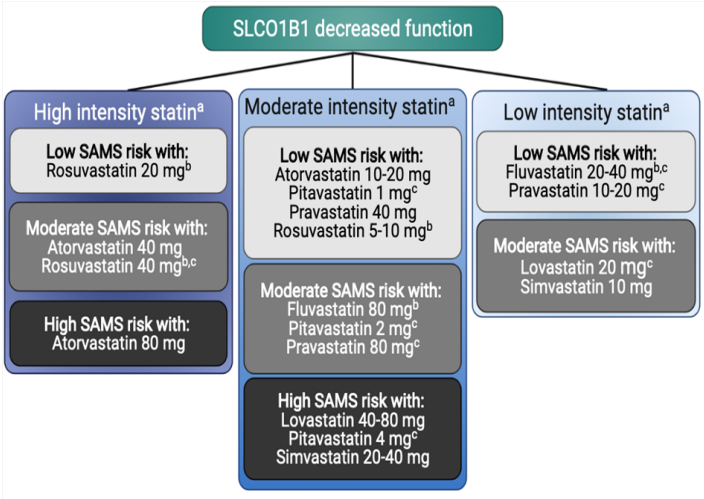
Therapeutic Recommendations

The Clinical Pharmacogenetics Implementation Consortium (CPIC) updated statin PGx guidelines in 2022, to include statin recommendations based on SLCO1B1 phenotype (i.e., decreased or poor function) for all statins (updated from only simvastatin).[3] CPIC recommendations are intended to align with American College of Cardiology and the American Heart Association (ACC/AHA) guidelines[4] by stratifying based on statin intensity for the two phenotypes, as shown in the **Figures 1 & 2**. Statin and statin doses indicated in the light grey boxes can be prescribed with the lowest risk for SAMS. Statin and statin doses indicated in dark grey boxes should be used with caution due to a possible increased risk for SAMS. Statin and statin doses indicated in black boxes should be avoided as the available evidence strongly suggests that they are associated with increased risk of harm.

Guidance for Patients Already on Statin Therapy

For patients who have been on a stable statin/dose for at least 4 weeks (for moderate SAMS risk) or at least 1 year (for high SAMS risk), without any symptoms of SAMS, may continue that statin/dose long term.[3] If they have been on therapy for less than 4 weeks (for moderate SAMS risk) or less than 1 year (for high SAMS risk), then clinicians may consider changing to a lower SAMS risk statin/dose in order to prevent the development of SAMS.[3]

Figure 1 | SLCO1B1 decreased function phenotype stratified by preferred statin intensity and dose[3,4]



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Practical Application

ST is a 67 yo Caucasian female with a PMH significant for hyperlipidemia, requiring a moderate intensity statin in accordance to the ACC/AHA guidelines. She was recently prescribed lovastatin 40 mg daily. After 3 weeks of lovastatin therapy, ST began to experience mild symptoms of muscle pain, where she was subsequently referred for PGx testing to guide appropriate statin and statin dose selection.

Her pharmacogenetic test results are as follows:

- *SLCO1B1* genotype: *5/*5
- SLCO1B1 phenotype: Poor function (!)

ST's pharmacogenetic test result indicate that she has poor function of SLCO1B1 hepatic transporter. The resulting poor hepatic uptake of the active form of lovastatin (lovastatin acid) would increase her systemic exposure by more than 200% compared to someone with SLCO1B1 normal function. According to CPIC guidelines, strong evidence suggests lovastatin 40-80 mg is associated with an increased risk for SAMS in SLCO1B1 poor function phenotypes (**Figure 2**, as indicated by the black box in the moderate intensity category). The recommendation is to switch lovastatin to an alternative statin associated with reduced SAMS risk, while remaining in the moderate intensity category. Moderate intensity statins, such as atorvastatin 10-20 mg or rosuvastatin 5-10 mg (**Figure 2**, as indicated by the light grey box in the moderate intensity category), have the lowest SAMS risk for poor function *SLCO1B1* genotype. If a high intensity statin is needed in the future, rosuvastatin may be titrated to 20 mg and has the strongest evidence for safe use in patients with poor SLCO1B1 function.

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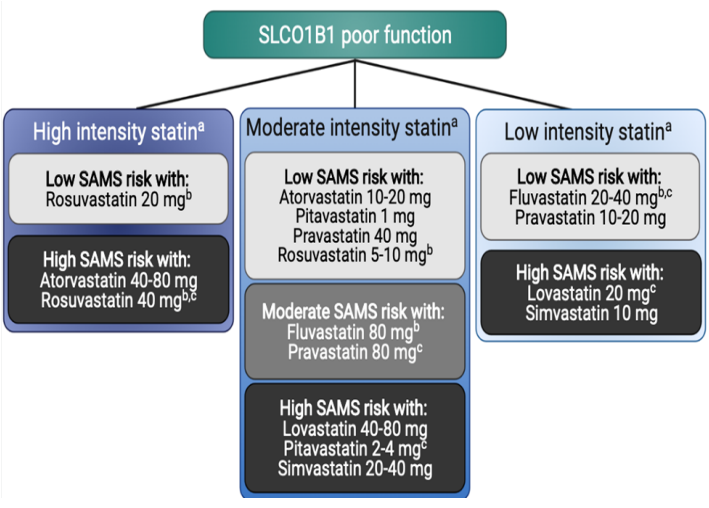
Figure 2 | SLCO1B1 poor function phenotype stratified by preferred statin intensity and dose[3,4]



Clinical Conundrums

Determining Insurance Coverage for PSCK9 Inhibitors

Christie Monahan, PharmD

PCSK9 inhibitors are powerful LDL-lowering medications used in combination with other lipid lowering medications for adults with known heart disease for secondary prevention or primary prevention for those with heterozygous familial hypercholesterolemia. Currently there are two medications on the market within the United States available for use, this includes Repatha® (evolocumab) and Praluent® (alirocumab).[1]

While both medications work similarly to reduce LDL, there are slight differences to consider when prescribing for a patient, including price, administration, and side effects. Both medications are administered via subcutaneous injection on an every two week or monthly schedule[1]. Repatha® is available through use via prefilled syringe, autoinjector (for use see pages 8-9), and infusor pump. Doses in both the prefilled syringe and autoinjector include 140mg/mL with usual dosing at 140mg every two weeks or 420mg every month. Use of the infusor pump occurs as a monthly administration at 420mg/3.5mL via infusor that is placed on the body for a period of 5 minutes then removed.[2]

In contrast, Praluent® is only available via autoinjector in two strengths, 75mg/mL or 150mg/mL. The usual dosage consists of 75mg administration every two weeks or 300mg every month (can be given in 150mg doses every two weeks).[3]

In addition, Repatha® is approved for use in children aged 10 years and older while Praluent® use is only approved for adults.[2] Side effects of both medications include injection site reactions, diarrhea, and muscle pain. Use is not indicated in pregnancy and caution is advised. Continued diet and exercise should be used in combination with PCSK9 inhibitors.[1]

Unfortunately use of PCSK9 inhibitors may not be as prevalent due to associated costs incurred by the patient. Many insurances will require step therapy prior to approval for use, meaning other medications (statins, ezetimibe, etc) will need to have documented trial and failure within the patient history. Oftentimes this clinically comes across as a prior authorization with needed explanation for use and chart notes with indications of failed treatment.

Clinical Conundrums

In addition, most insurances will prefer one of the two medications available, but may not cover both. Evaluating the insurance formulary by searching online or contacting the local pharmacy can help to determine which medication is on formulary for the patient. Once the determination is made as to which medication is covered, an active prescription must be sent to desired pharmacy to determine patient copay.

Currently copay assistance options are available for both Repatha® and Praluent® for Medicare, Medicaid, and commercially insured patients (see **Table 1**). Out-of-pocket costs with use of the GoodRx® Savings Card costs $536-$580 for Repatha®[4] and $480-$526 for Praluent®[5]. Medicare Part D patients may be eligible for patient assistance programs through drug manufacturer based on income requirements. In addition, if medication is not preferred on formulary, physicians are able to submit appeal or request for drug addition to formulary with explanation of patient -specific circumstances.

Additional Clinician Resources

NeedyMeds.org

- Centralized resource for clinicians to determine copay assistance (copay cards, patient assistance) availability for a variety of medications
- Able to download necessary forms from one site

FormularyLookup.com

- Centralized resource for clinicians (must have NPI) to determine medication coverage based on state and insurance plan
- Available for download via app on phone

References

1. Grundy, Scott M., et al. "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." Circulation, vol. 139, no. 25, 2019, https://doi.org/10.1161/cir.0000000000000625.
2. High Cholesterol (LDL-C) Treatment | Repatha® (evolocumab). www.repatha.com. Accessed March 1, 2023. https://www.repatha.com/
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5. Repatha Prices, Coupons & Savings Tips—GoodRx. www.goodrx.com/praluent. Accessed March 5, 2023.
6. Patient and Practice Support | Repatha® (evolocumab). www.repatha.com. Accessed March 1, 2023. https://www.repatha.com/
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Table 1 | PCSK9 Inhibitor Coverage by Insurance*

Insurance Type	Evolocumab (Repatha®)	Alirocumab (Praluent®)
Medicare	Yes	Yes
	1 supply of 2 pens (140mg/mL) per month $95—$1,201[a]	1 supply of 2 pens (75mg/mL) per month $265—$1,227[a]
Medicaid	Step Program Required Coverage varies by state	Step Program Required Coverage varies by state
	$0—$50	
Commerical	Yes Copay Card Available $5 per month[b]	Yes Copay Card Available $25 per month[d]
Uninsured	Amgen Safety Net Foundation Patient Assistance Program[c] $0	MyPRALUENT Patient Assistance Program[c] $0

* Subject to change yearly with formulary; [a]Dependent on deductible and coverage at time of fill; [b]No income requirements, maximum monthly benefit determined by insurance plan; [c]Must live within the United States and meet household income requirements, some Medicare Part D members may be eligible; [d]No income requirements, maximum assistance of $3,500 per year

Over-the-Counter

Smell A Little Fishy? Evaluating OTC Fish Oil Products

Christie Monahan, PharmD

Diet modification and exercise are recommended as first line non-pharmacologic treatment options for hyperlipidemia, followed by prescription medications if needed. While these recommendations are provided, many patients are unaware of the type of foods with natural healthy fats and may turn to supplementation with over-the-counter products. This overview is intended to evaluate the different types of omega-3 compounds commercially available and assist in determining the appropriate type of supplement to recommend for patients.

Omega-3s are important components of the membranes that surround each cell in the body and are found in foods, such as fish and flaxseed, and in dietary supplements, such as fish oil. This type of omega has been shown to reduce risk of cancer, heart disease and diabetes.[1]

The three main components of omega-3 fatty acids are alpha -linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA is found mainly in plant oils such as flaxseed, soybean, and canola oils while DHA and EPA are found in fish and other seafood. ALA is an essential fatty acid and must be attained through dietary sources whereas the body can convert some ALA into EPA and then to DHA in very small amounts. Therefore, getting EPA and DHA from foods (and dietary supplements if necessary) is the only practical way to increase levels of these omega-3 fatty acids in the body for cardiovascular protection.[1] Experts have not established recommended daily amounts for all omega-3 fatty acids, with the exception of ALA (see **Table 1**).[2]

The American Heart Association (AHA) currently recommends eating one to two servings of seafood per week to reduce cardiovascular risk. For people with heart disease, the AHA recommends consuming about 1 g per day EPA plus DHA, preferably from oily fish. In addition, the AHA does not currently recommend omega-3 supplements for people who do not have a high risk of cardiovascular disease.[1] For patients with allergies to seafood or dislike of natural sources of omega-3, over-the-counter supplementation is available.

Common omega-3 dietary supplements include fish oil, krill oil, cod liver oil, and algal oil (a vegetarian source that comes from algae). Each providing a wide range of doses and forms of …

Table 1 | Daily Recommended Intake of Alpha-Linolenic Acid (ALA) by the American Heart Association[2]

Life Stage	Recommended Amount of ALA (grams)
Birth to 12 months	0.5
Children 1-3 years	0.7
Children 4-8 years	0.9
Boys 9-13 years	1.2
Girls 9-13 years	1.0
Teen boys 14-18 years	1.6
Teen girls 14-18 years	1.1
Men	1.6
Women	1.1
Pregnant teens and women	1.4
Breastfeeding teens and women	1.3

Figure 1 | NatureMade® 1200mg Fish Oil Softgel Label[3]

Over-the-Counter

… omega-3s. The U.S. Food and Drug Administration (FDA) recommends consuming no more than 5 g/day of EPA and DHA combined from dietary supplements. Side effects from taking omega-3 supplements are usually mild, but may include an unpleasant taste in the mouth, bad breath, heartburn, nausea, stomach discomfort, diarrhea, headache, and smelly sweat. Oftentimes the unpleasant "fish burp" with supplementation can be negated with storage in the fridge prior to administration. In addition, omega-3 dietary supplements may interact with the medications. For example, high doses of omega-3s may cause bleeding problems when taken with warfarin or other anticoagulant medicines.[1]

Patients should get most of their nutrients from food and beverages, according to the federal government's Dietary Guidelines for Americans. Natural foods contain vitamins, minerals, dietary fiber, and other components that benefit overall health. In some cases, fortified foods and dietary supplements are useful when it is not possible to meet needs for one or more nutrients (for example, during specific life stages such as pregnancy).[1] Patients should be encouraged to read the food label on the back of all supplements for determination of serving size (oftentimes more than one capsule alone) and EPA/DHA content (see **Figure 1**[3]). In addition, verifying the product was tested in an FDA registered laboratory and free of chemicals is also recommended. Average price for OTC fish oil $6 to $30 dependent on quantity of capsules and potency of product.

If patients are struggling to afford, administer, or at clinically elevated risk of cardiovascular event while on a maximum tolerated statin, prescription fish oil derivatives are available. Icosapent ethyl (Vascepa®) has been shown to lower chance of heart…

Over-the-Counter

… attack or stroke by 25% in patients on maximum tolerated statin with triglycerides greater than 125mg/dL and established CVD or diabetes.[4] In contrast, omega-3 acid ethyl esters (Lovaza®) serves as a high-potency 1 g capsule containing 465mg EPA and 375mg DHA.[5] Both medications are used to reduce very high triglycerides (>500mg/dL) and should be used in addition to diet and exercise.[4,5]

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Device Debrief

Repatha® SureClick® Autoinjector

Christie Monahan, PharmD

Repatha® (evolocumab) is a novel PCSK9 inhibitor that functions to reduce cholesterol in patients with known cardiovascular risk or patients with a family history of familial hypercholesteremia. The medication works as a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein receptors (LDLR) on hepatocyte surfaces to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL; therefore, the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-cholesterol (LDL-C). By inhibiting the binding of PCSK9 to LDLR, evolocumab increases the number of LDLRs available to clear LDL from the blood, thus lowering serum LDL-C levels.[1]

Evolocumab is administered subcutaneously every 2 weeks or monthly as directed. Drug metabolism reaches peak concentration in 3-4 days with a half-life of 11-17 days. Side effects are minimal but may include injection site reaction, myalgias, and headache. Patients should be cautioned against use of this medication if they have experienced a hypersensitivity to evolocumab or its excipients in the past. Of note, this injection does contain polysorbate. Routine monitoring of lipid profile should be performed prior to starting treatment and rechecked in 4 to 12 weeks.[1]

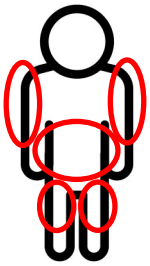
Dosing of evolocumab is independent of patient response. Dosing starts at 140mg every 2 weeks or 420mg once monthly. Clinical recommendations advised to start with biweekly dosing administration if event of hypersensitivity reaction occurs. Patients may increase to 420mg every 2 weeks if no clinically meaningful response is achieved within 12 weeks of use.[1]

Patients have the option of desired dosing device: prefilled syringe, autoinjector, or single-use infusor. The following graphics (see **Figures 1-6**) will depict administration of evolocumab via the SureClick® autoinjector. The autoinjector is dispensed with two 140mg pens per pack, total use for 30 days. The patient should inject the contents of one pen every 2 weeks. Prior to first use, the patient should be sure to keep the medication refrigerated.[2]

Device Debrief

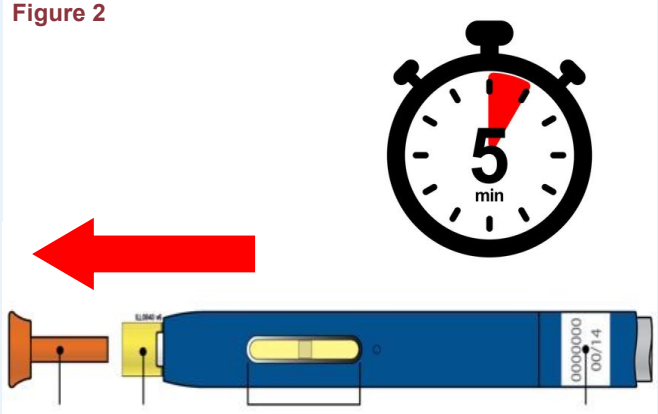
When ready for use, allow to stand at room temperature for at least 30 minutes (do not warm with heat or hot water).[2] This allows the medication to warm and feels better when injected under the skin.

Figure 1



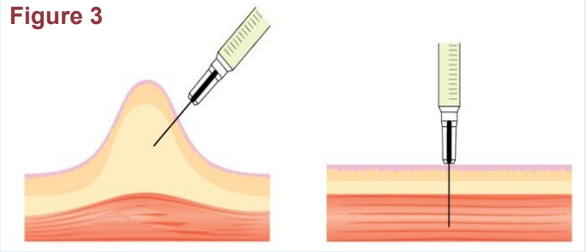
Prep the site of administration with alcohol or warm water and soap to ensure the area is clean. Administer into areas of the abdomen (except for the 2-inch area around the navel), thigh, or upper arm (**Figure 1**). Avoid administration in areas where skin is tender, bruised, red, indurated, or has scars or stretch marks. Do not coadminister with other injectable drugs at the same injection site. Patient should be advised to rotate the injection site with each injection. Once the area is prepped, the patient must remove the orange cap and ensure the medication is injected within 5 minutes of opening (**Figure 2**).[2]

Figure 2



To administer the medication, stretch or pinch the injection site to create a firm surface (**Figure 3**) making sure to inject in the fatty tissue. Injection into the muscle may lead to increase bruising and pain with injection.[2]

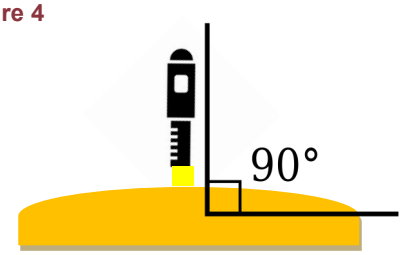
Figure 3



Device Debrief

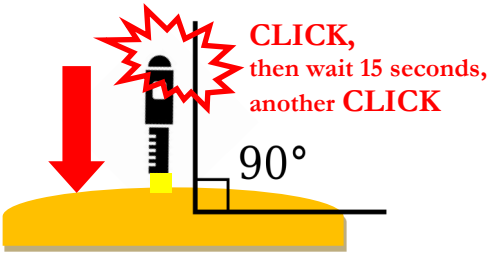
Instruct the patient to press the pen with yellow safety guard tip to the skin at a 90 degree angle to administer the drug (Figure 4).[2]

Figure 4



Once the yellow safety guard is flush with the skin, the patient should firmly press down on the skin and push the grey start button; an audible click will be observed (Figure 5). This is indicating the medication is being administered and the patient should hold for 15 seconds.[2]

Figure 5



Once the clear window turns to yellow and another audible click is heard, the medication has been completely administered (Figure 6) and the device should be discarded in the sharps container (or hard plastic bottle sealed with tape and thrown into trash) due to the presence of a small needle (27 gauge, 0.5 inch long).[2]

Figure 6

If patients have any concerns or questions regarding how to give the injection, help is available at their local pharmacy or by calling the Repatha*Ready*® Nurse (1-844-REPATHA). Additional information may also be found online.[1]

References:

1. High Cholesterol (LDL-C) Treatment | Repatha® (evolocumab). www.repatha.com. Accessed March 5, 2023.
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Drug Update:
New Indications and Dosage Forms
March 2023

Leqembi® (lecanemab-irmb) Injection
New Molecular Entity: Indicated for treatment of Alzheimer's disease with the presence of amyloid bodies; medication is an amyloid beta-directed antibody indicated for use in patients with mild cognitive impairment or dementia; administered over one hour infusion every two weeks

Brenzavvy® (bexagliflozin) Tablet
New Molecular Entity: SGLT2 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes

Jesduvroq® (daprodustat) Tablets
New Molecular Entity: Indicated for treatment of anemia secondary to chronic kidney disease in adults who have been receiving dialysis for at least four months; functions as a hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor used in place of ESA therapy; black box warning for increased death and thrombosis; not for use in patients with preexisting heart failure

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