Statin Recommendations by Risk Group

Executive Summary: Indication for statin therapy is relatively clear for patients in certain management groups (secondary prevention, severe hypercholesterolemia and diabetes). For other patients with elevated LDL-C cholesterol outside of these management groups, the decision whether or not to initiate statin therapy can be more challenging. Start with calculating a 10-year ASCVD risk by using the ASCVD Risk Estimator Plus to establish the patient's initial risk category. For patients that fall into the Intermediate Risk category further evaluation with a Coronary Artery Calcium (CAC) score and applying that score to a MESA calculator can be used to better define a patient's risk.

Key Take-Home Messages from the 2018 Guideline on the Management of Blood Cholesterol

Patient Management Groups	Statin Recommendation		Comments
Secondary ASCVD Prevention	High-intensity statin		· 75 years of age or younger · Goal LDL-C reduction ≥50% · Goal LDL-C <70 mg/dL in very high risk
Severe hypercholesterolemia (LDL-C ≥190 mg/dL)	High-intensity statin		· 20-75 years of age · Goal LDL-C reduction ≥50%
Diabetes Mellitus	Moderate-intensity statin		· 40-75 years of age
	High-intensity statin		· 40-75 years of age with multiple ASCVD risk factors
Adults 40-75 years of age, LDL-C ≥70-<190 mg/dL, without diabetes*†‡	Low Risk (<5%)	No statin	
	Intermediate Risk (7.5% - <20%)	Moderate-intensity statin	· Use a CAC score and MESA calculation to re-classify patient risk to help determine initiation of statin therapy
	High Risk (≥20%)	High-Intensity Statin	· Goal LDL-C reduction ≥50%

*Use the race- and sex-specific ASCVD Risk Estimator Plus to estimate the 10-year ASCVD risk as the first step in determining a patient's risk and consideration for statin therapy

†In general, obtaining CAC scores should be limited to those in the Intermediate Risk category due to lower benefit to risk ratio and higher costs in Low and High Risk categories.

‡HOPE-3 RCT provides additional support for this recommendation since the initial recommendation in the 2013 ACC/AHA guidelines – moderate intensity statin produced a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without ASCVD

ASCVD Risk Estimator Plus

- Important starting point, but does not necessarily provide the final decision for or against statin use due to limitations
    - Age is a powerful population risk factor and dominates risk scoring with advancing age; but does not necessarily reflect individual risk
    - Limited data on use in adults <40 years of age
    - Less accurate in risk prediction in patients already receiving intensive preventive efforts, may overestimate risk
    - Limited data on other racial/ethnic groups which may overestimate risk

- May overestimate or underestimate the risk of those within the Intermediate Risk category
    - Patients in the Intermediate Risk category should be further assessed with a CAC score and calculation of a MESA 10 year risk score

Coronary artery calcium (CAC) Measurements and MESA Scoring

A CAC score predicts ASCVD events and is independent of other risk factors such as age, sex and ethnicity. Adding a CAC to other risk factors (MESA CHD Risk Estimator) can greatly improve risk stratification and better guide initiation of statin therapy discussions.

- Patients who may benefit from CAC scoring…
    - Patients that are at Intermediate Risk category on the ASCVD Risk Estimator Plus
    - Patients reluctant to initiate statin therapy who wish to understand the risk and potential benefit more precisely
    - Older patients with low burden of risk factors who question whether they would benefit from statin therapy
    - Patients with ASCVD Risk Estimator Plus calculated 10-year risk < 7.5%, and have risk factors that are not included in the calculation (e.g. strong family history of ASCVD)
- Professional society guidelines recommend:
    - CAC score = 0: treatment with statin therapy may be withheld or delayed (NNT of 154)
    - CAC score 1-99: favors statin therapy
    - CAC score ≥ 100: statin therapy is indicated (NNT of 30)

Monitoring

- Assess adherence and percentage response to LDL-C lowering medications with a repeat lipid measurement 4-12 weeks after statin initiation or dose adjustment and repeat as needed to assess adherence
- Assess liver function tests at baseline and at 4-12 weeks after statin initiation
- Creatine Kinase only if clinically indicated

Recommendations for older adults

- Many randomized studies on statins exclude elderly patients. However, there are meta-analyses of elderly patients in statin trials that show significant reductions in cardiovascular outcomes for patients over 75 years of age.
- The absolute benefit decreases with age due to the fact that death from all causes increases with age. The absolute benefit in patients with a life expectancy less than 5 years and over age 85 is likely small.

References:

1. Grundy SM, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):3168-209.
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Managing Statin-Associated Muscle Symptoms

Executive Summary: Statin intolerance related to statin-associated muscle symptoms (SAMS) is a common cause for statin nonadherence and discontinuation, however the frequency of SAMS has been found to be the same in patients treated with a statin as a placebo. It is recommended to assess for the likelihood of SAMS and rechallenge as appropriate. When rechallenging statin therapy, consider restarting the same statin at a lower dose, dosing the statin every other day, or selecting an alternate statin with lower incidence of SAMS such as rosuvastatin, pravastatin or fluvastatin. Use of vitamin D or coenzyme Q10 is not recommended for SAMS.

Predisposing factors for Statin-Associated Muscle Symptoms (SAMS)

- Female sex
- Low body mass index
- Comorbidities (HIV, renal, liver, thyroid, preexisting myopathy)
- Asian ancestry
- Excess alcohol
- High levels of physical activity
- Trauma

Frequency of SAMS

- Less frequent in randomized controlled trials (1-5%)
- More frequent in observational studies and clinical setting (5-10%), suggesting a "nocebo effect" in which the patient's negative thinking impacts health
    - This effect was recently evaluated in the SAMSON trial, which found that there was no difference in symptom scores or discontinuation when study participants took atorvastatin or placebo

Assessment

- Consider using the National Lipid Association's Statin Myalgia Clinical Index Score to determine likelihood of SAMS and to assess response to rechallenge
    - Use in patients with muscle symptoms that were new or increased after starting a statin regimen
    - Muscle symptoms may include aches, cramps, heaviness, discomfort, weakness, or stiffness
    - Assess for other possible causes of muscle symptoms such as recent physical exertion, changes in exercise patterns, hypothyroidism, drug interaction with statin, concurrent illness, underlying muscle disease
        - Differentiate with common conditions with similar presentation such as OA, RA, tendinitis and chronic pain disorders
        - Drug interactions may include gemfibrozil, cyclosporine, fibrates and CYP3A4 inhibitors (e.g., clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, and verapamil)

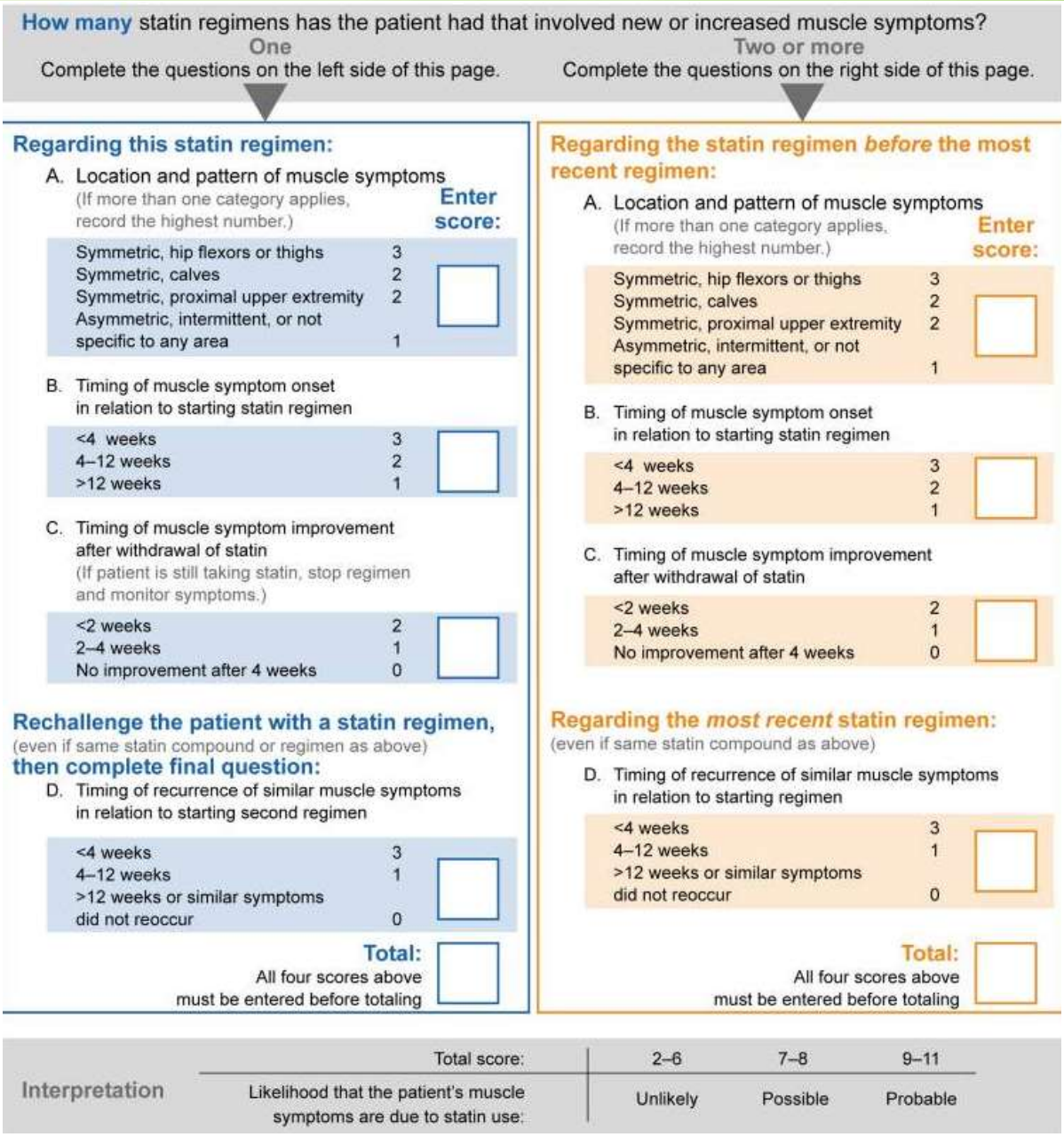
Statin Rechallenge – Discontinue the statin and wait for symptom resolution

- Reinitiate a statin regimen after a minimum 2-week statin-free period

    - Modify the dosing regimen, restart the same statin at a lower dose or consider every-other-day statin therapy
    - Use an alternate statin – a hydrophilic statin (rosuvastatin or pravastatin), or fluvastatin
    - Use a statin in combination with non-statin therapy
- Use of vitamin D and coenzyme Q10 are not supported by RCTs

Severe SAMS

- Measure creatine kinase
- If symptoms are suggestive of hepatotoxicity, also measure liver transaminases, total bilirubin, and alkaline phosphatase
- In patients with severe SAMS or recurrent SAMS despite appropriate statin rechallenge, consider proven non-statin therapy that is likely to provide cardiovascular benefit



How many statin regimens has the patient had that involved new or increased muscle symptoms?

One
Complete the questions on the left side of this page.

Two or more
Complete the questions on the right side of this page.

Regarding this statin regimen:

A. Location and pattern of muscle symptoms
(If more than one category applies, record the highest number.)

		Enter score:
Symmetric, hip flexors or thighs	3	
Symmetric, calves	2	
Symmetric, proximal upper extremity	2	
Asymmetric, intermittent, or not specific to any area	1	

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3	
4–12 weeks	2	
>12 weeks	1	

C. Timing of muscle symptom improvement after withdrawal of statin
(If patient is still taking statin, stop regimen and monitor symptoms.)

<2 weeks	2	
2–4 weeks	1	
No improvement after 4 weeks	0	

Rechallenge the patient with a statin regimen,
(even if same statin compound or regimen as above)
then complete final question:

D. Timing of recurrence of similar muscle symptoms in relation to starting second regimen

<4 weeks	3	
4–12 weeks	1	
>12 weeks or similar symptoms did not reoccur	0	

Total: All four scores above must be entered before totaling

Regarding the statin regimen *before* the most recent regimen:

A. Location and pattern of muscle symptoms
(If more than one category applies, record the highest number.)

		Enter score:
Symmetric, hip flexors or thighs	3	
Symmetric, calves	2	
Symmetric, proximal upper extremity	2	
Asymmetric, intermittent, or not specific to any area	1	

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3	
4–12 weeks	2	
>12 weeks	1	

C. Timing of muscle symptom improvement after withdrawal of statin

<2 weeks	2	
2–4 weeks	1	
No improvement after 4 weeks	0	

Regarding the *most recent* statin regimen:
(even if same statin compound as above)

D. Timing of recurrence of similar muscle symptoms in relation to starting regimen

<4 weeks	3	
4–12 weeks	1	
>12 weeks or similar symptoms did not reoccur	0	

Total: All four scores above must be entered before totaling

Interpretation

Total score:	2–6	7–8	9–11
Likelihood that the patient's muscle symptoms are due to statin use:	Unlikely	Possible	Probable

References:

1. Grundy SM, 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. 2019;73(24):3168-209. https://doi.org/10.1161/CIR.0000000000000625
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Use of Non-Statin Cholesterol Lowering Agents

Executive Summary: Non-statin therapy is generally not recommended first line for reducing cardiovascular morbidity and mortality. Ezetimibe, PCSK9 inhibitors and bempedoic acid may be considered for add-on therapy when LDL-C is not at goal with maximally tolerated statin. Due to lower cost and good efficacy, ezetimibe is the preferred add-on for patients who are not meeting lipid goals with a maximally tolerated statin. PCSK-9 medications and bempedoic acid can also be considered as an add-on but are more expensive. Fenofibrate can be used in patients with severely elevated triglycerides despite maximally tolerated statin to decrease risk of pancreatitis, but have no evidence of reducing ASCVD outcomes. Bile acid sequestrants and niacin should be avoided due to common side effects and lack of clinical benefit in reducing ASCVD in combination or monotherapy.

Non-statin medication use pearls

- Prior to adding on non-statin therapy assess and reinforce lifestyle changes and adherence to statin therapy.
    - Assess and reinforce adherence to statin therapy
    - Assess and reinforce lifestyle changes
    - Check for secondary causes of elevated LDL or triglyceride (diabetes, cholestatic liver disease, nephrotic syndrome, chronic kidney disease, hypothyroidism, excessive alcohol use, medications).
- Ezetimibe
    - Preferred initial add-on for most patients not meeting lipid goals with high dose or maximally tolerated statin
    - IMPROVE-IT assessed the incidence of major CV events in patients treated with ezetimibe and simvastatin vs. simvastatin alone
        - Patients were started on simvastatin doses of 40mg daily but could be titrated to 80mg if LDL-C remained above 79 mg/dL
        - Lower rate of the primary composite cardiovascular outcome seen with ezetimibe and simvastatin combination (HR 0.94, 95% CI 0.89-0.99)
- PCSK9 inhibitors
    - Consider as add-on for patients not meeting lipid goals with high dose or maximally tolerated statin plus ezetimibe
    - Can consider addition of PCSK9-inhibitor prior to adding on ezetimibe, however this is less cost effective therapy
    - Subcutaneous injection (every 2 or 4 weeks)
    - Do not appear to cause muscle toxicity or elevated liver enzymes
    - Mild local injection site reactions are the most commonly reported adverse effects
- Bempedoic Acid
    - Inhibitor of adenosine triphosphate citrate lyase, an enzyme upstream from HMG-CoA reductase – the target in statins
    - Approved in 2020 to be used with maximally tolerated statin for the treatment of adults with heterozygous familial hypercholesterolemia or ASCVD who require additional lowering of LDL-C

        - In the study population of patients already on statin it lowered the LDL-C by about 20 points (or 15%) from baseline
        - LDL-C lowering may be more pronounced in patients on concomitant low- to moderate-intensity statins compared to those on high-intensity statins
    - Common adverse events include gout, hyperuricemia, myalgia, upper respiratory tract infection, leukopenia and anemia
        - Measure uric acid and stabilize gout before initiating
- Fibric Acid
    - Preferred add-on for patients with hypertriglyceridemia that are on high dose or maximally tolerated statin when triglycerides are not at goal.
    - Avoid use of gemfibrozil in combination with any statin due to myopathy risk
    - Fenofibrate is preferred over gemfibrozil for treating elevated triglycerides to prevent pancreatitis
    - Mild LDL-lowering, no cardiovascular clinical evidence to support use as an add-on to statin therapy or monotherapy for hypercholesterolemia
- Omega-3 Fatty Acids
    - Consider as add on for patients with hypertriglyceridemia not meeting goals on maximally tolerated statin and/or fibric acid agent
    - Icosapent ethyl preferred agent, especially in patients with known ASCVD or at very high risk for ASCVD, due to evidence that may support reducing cardiovascular outcomes
- Bile Acid Sequestrants
    - Consider as an add-on for patients not meeting lipid goals with a statin, do not tolerate ezetimibe, and cost is an issue for PSK9 Inhibitors or Bempedoic acid
    - May be difficult to tolerate due to GI side effects including constipation and gas
    - Cholestyramine can have major drug interactions which impacts timing of dosing
    - No evidence of reducing ASCVD outcomes
- Niacin
    - Can raise HDL-C levels, however not recommended to use for that indication
    - Poorly tolerated, causing flushing, pruritis, paresthesias, nausea, hyperglycemia and hyperuricemia
    - Mild LDL-lowering, no clinical evidence to support use as an add-on to statin therapy or monotherapy for hypercholesterolemia

Effects of non-statin lipid-lowering drugs on serum lipid levels			
Medication/Class	**LDL-C (% change)**	**HDL-C (% change)**	**Triglycerides (% change)**
Ezetimibe	↓ 17%	↑ 1%	↓ 7-8%
Bile Acid Sequestrants	↓ 15-30%	0%	0%
PCSK9 inhibitors	↓ 38-72%	↑4-9%	↓2-23%
Fibric acid – fenofibrate	↓ 6-20%	↑ 5-20*%	↓ 41-53%
Fibric acid – gemfibrozil	↓ 10-15%	↑ 5-20*%	↓ 35-50%
Niacin	↓ 10-25%	↑ 15-35%	↓ 25-30%
Bempedoic acid	↓15-19%	0 to ↓ 4.5%	0%

*Increases of 20% are seen in patients with very high triglycerides; increases of 5% are more typical in patients with lower triglycerides

References:

1. Grundy SM, 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. 2019;73(24):3168-209. https://doi.org/10.1161/CIR.0000000000000625
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Cardiovascular Benefit of Omega-3 Supplementation

Executive summary: Omega-3 fatty acids are often prescribed to patients with hypertriglyceridemia to lower triglyceride levels. Although they lower triglyceride levels in a dose dependent manner, their clinical effects on cardiovascular events is less clear. Omega-3 fatty acids are not currently recommended to treat cardiovascular disease alone, but should be considered for treatment of significantly elevated triglycerides despite statin use. Icosapent ethyl may provide additional cardiovascular benefit and should be considered as the preferred agent. Weigh risk vs. benefit as RCTs have found an increased risk of new onset atrial fibrillation with omega-3 fatty acids.

Increased intake of omega-3 fatty acids has been associated with a reduced risk of cardiovascular disease in observational studies, but this finding has not been confirmed in randomized trials. It remains unclear whether this supplementation has cardiovascular benefit and if use should be encouraged for the sole purpose to reduce cardiovascular events.

STRENGTH (2020):

- 4 grams per day of Omega-3 fatty acids (EPA & DHA) po once daily versus matching corn oil placebo
- Significantly increased **risk of new onset atrial fibrillation**
- **No significant difference** seen in major adverse cardiovascular events

REDUCE-IT (2019)

- 2 g icosapent ethyl (EPA) po BID versus matching mineral oil placebo
- Limitation: mineral oil produces a significant increase in LDL cholesterol and high-sensitivity C-reactive protein
- Significantly increased **risk of new onset atrial fibrillation**
- Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was **significantly lower** among those who received 2 g icosapent ethyl twice daily than among those who received placebo

ASCEND (2018)

- 1 g per day of omega-3 fatty acids (EPA & DHA) versus matching olive oil placebo
- There was **no significant difference** in the risk of serious vascular events between those who were assigned treatment or placebo among patients with diabetes without evidence of cardiovascular disease

OMEMI (2020)

- Specifically looked at elderly patients with recent acute myocardial infarction (AMI)
- 1.8 g omega-3 fatty acids (EPA & DHA) po once daily versus corn oil
- There was **no significant difference** in clinical events in elderly patients with recent AMI who were treated with 1.8 g of omega-3 fatty acids once daily for 2 years

Takeaways

- The recommendation of using omega-3 fatty acids to reduce the incidence of cardiovascular events is still under investigation
- In the absence of hypertriglyceridemia, omega-3 fatty acids should not be started
    - Significantly elevated triglycerides (>500 mg/dL) should be treated first line with statin therapy
    - If triglycerides remain elevated despite maximally tolerated statin therapy, consider the addition of omega-3 fatty acids
    - Icosapent ethyl may have more benefit for cardiovascular benefits than fibrates – weigh risk vs. potential benefits of each therapy when developing plan for hypertriglyceridemia
- The REDUCE-IT trial utilized an unequal placebo, mineral oil. In REDUCE-IT, researchers used 4 g daily mineral oil placebo as the comparator. This resulted in significant adverse effects and a mean 11.4% increase in LDL cholesterol and mean 32.3% increase in high-sensitivity C-reactive protein.
- In the STRENGTH trial, utilizing corn oil, researchers saw a mean 1.1% decrease in LDL cholesterol and a mean 6% decrease high-sensitivity C-reactive protein.
- EPA levels in the REDUCE-IT trial were higher than in the STRENGTH trial. Although the STRENGTH trial used combination EPA-DHA resulting in relatively lower levels, the blood levels of EPA in the plasma and red blood cells remained high due to the carboxylic acid formulation allowing greater bioavailability. Researchers are uncertain whether or not these differences could lead to a significantly different result.

Fish Oil-OTC versus icosapent ethyl (Vascepa)-Rx

- Icosapent ethyl is an omega-3 fatty acid, similar to those found in a fish oil supplement bought over-the-counter. Unlike icosapent ethyl which contains only eicosapentaenoic acid (EPA), over-the-counter fish oil supplements generally contain two different kinds of omega-3 fatty acids, EPA and docosahexaenoic acid (DHA).
- EPA is the omega-3 fatty acid that is generally attributed to benefits with hypertriglyceridemia and cardiovascular health.
- Some studies have found that DHA may have some counteractive effects with EPA.
- Icosapent ethyl is available in a 0.5 gram dose and a 1 gram dose. Generic is available only in the 1 gram formulation.

Guideline Recommendations

- More studies need to be done to determine the place in therapy for fish oil supplementation
- There are no recommendations within the 2018 ACC/AHA guidelines for the use of fish oil supplementation for any indication

References:

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