VA/DoD Clinical Practice Guideline

Diagnosis and Management of Dyslipidemia for Cardiovascular Risk Reduction

Version 3.0

GUIDELINE SUMMARY 2014

VA/DoD Evidence Based Practice

Department of Veterans Affairs

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VA/DoD Clinical Practice Guideline

for

The management of Dyslipidemia for Cardiovascular Risk Reduction

Guideline Summary

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and

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Full guideline available at:

http://www.healthquality.va.gov *or* https://www.qmo.amedd.army.mil

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and The Department of Defense (DoD) guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when providers take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health care professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

Version 3.0 – 2014

DISCLAIMER

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts (all practicing clinicians), it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendations.

These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

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BACKGROUND

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in the United States (US) and globally. In Western countries, most CVD is due to atherosclerosis. [1] Atherosclerosis is the buildup of plaque (cholesterol, proteins, calcium and inflammatory cells) in the walls of arteries that carry oxygenated blood to the heart and other parts of the body. This plaque narrows the opening of the arteries, limiting the flow of oxygenated blood and increasing the risk of chronic and acute ischemia. If a plaque ruptures within a vital artery, a blood clot forms on the plaque and may obstruct the flow of oxygenated blood to the heart or brain, resulting in an acute coronary syndrome (ACS), myocardial infarction (heart attack; MI) or stroke with potentially irreversible damage to the tissue of the heart or brain.

Control and reduction of atherosclerotic cardiovascular disease (ASCVD) risk factors, including high cholesterol levels, elevated blood pressure (BP), insulin resistance, smoking and a sedentary lifestyle, can contribute to a reduction in ASCVD morbidity and mortality.

Dyslipidemia is defined as one or more of the following: low density lipoprotein cholesterol (LDL-C) >130 mg/dL, high density lipoprotein cholesterol (HDL-C) <40 milligram per deciliter (mg/dL), or triglyceride (TG) >200 mg/dL. [2] In patients with known CVD or high risk for CVD, even "normal" levels of lipids can be deemed amenable to intervention for the purpose of reducing CVD risk.

Dyslipidemia may remain clinically silent until the development of complications. This condition can be diagnosed with a blood test measuring plasma levels of total cholesterol (TC), HDL-C, TG, or individual lipoproteins. LDL-C is measured directly or determined by the following equation: TC-HDL-(TG/5). Sometimes, non-HDL cholesterol is also determined as TC minus HDL. A TC of less than 180 mg/dL is thought to be optimal. [3] Yet, the average TC for American adults is about 200 mg/dL. [4]

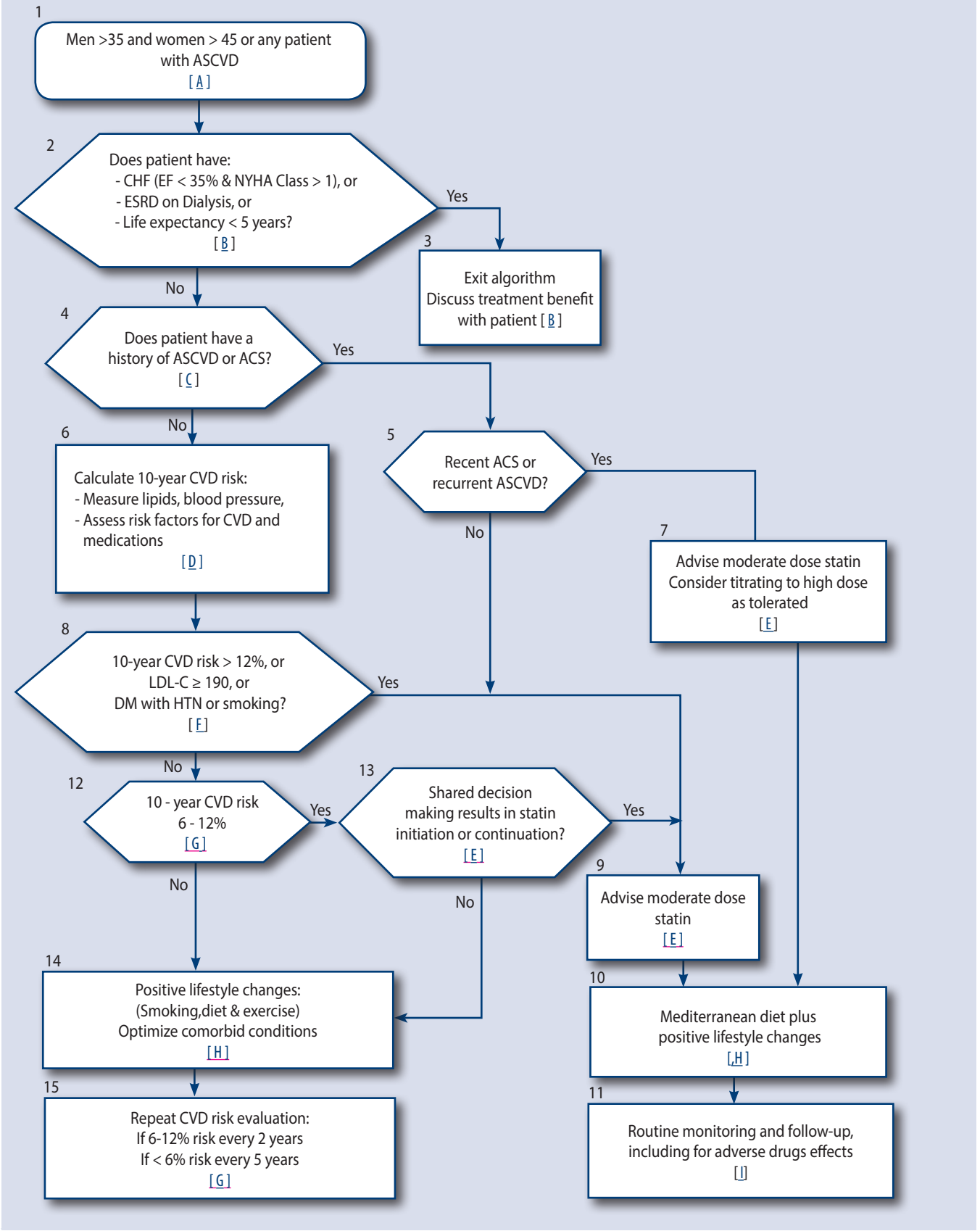
The etiology of dyslipidemia involves genetic, lifestyle and other factors. Genetic factors that result in either overproduction or slow clearance of TGs and LDL-C, or underproduction or fast clearance of HDL-C, can lead to dyslipidemia. A sedentary lifestyle with excessive dietary intake of saturated fat, trans fats, added sugars, and cholesterol can also lead to dyslipidemia. Other risk factors include insulin resistance, diabetes mellitus (DM or diabetes), central obesity, and chronic kidney disease (CKD).

About 71 million adults in the US (33.4%) have high LDL-C and only one out of every three adults with high LDL-C has the condition under control. [4]The percentage of American adults with high LDL-C has remained around 34 percent over the past decade, but treatment of high LDL-C has increased from 28.4 percent in 1999–2002 to 48.1 percent in 2005–2008. [4] Treatment usually involves dietary changes and lipid-lowering drugs. However, the management of dyslipidemia has shifted away from treating the dyslipidemia itself as a discrete entity, and moved toward managing dyslipidemia in the context of overall risk for CVD.

This guideline addresses the various treatment and management strategies for managing overall CVD risk among patients with dyslipidemia. As TG levels above 300mg/dl are above the 95th percentile, few patients in the US will have levels above 300mg/dl. Even fewer patients will have TGs >500mg/dl (99th percentile). Due to the infrequency of clinically significant hypertriglyceridemia this guideline does not address hypertriglyceridemia other than to look for secondary causes and non-pharmacologic interventions. Interested readers can refer to Lederle and Bloomfield's 2012 article for additional information. [5]

Algorithm

Management of Dyslipidemia



ASCVD and Equivalents

- All ACS and MI
- CABG or PCI
- Stable obstructive CAD (stable symptoms of angina or equivalent)
- CVA or TIA
- Atherosclerotic PVD (claudication or AAA)

Does not include asymptomatic atherosclerotic (CAC, exercise test, IMT, ABI, brachial reactivity)

Statin Dose (by 10-yr CVD Risk)

10-yr Risk	Statin Dose
ASCVD (2nd prevention)	Mod - Hi
>12 %	Mod
6-12 % (with SDM)	Mod
< 6 %	None

Statin Dose

	Moderate [mg]	High [mg]
Generic		
Atorvastatin	10-20	40-80
Simvastatin	20-40	-
Pravastatin	40	-
Lovastatin	40-80	-
Fluvstatin	80 (80 XL QD or 40 BID)	-
Brand		
Rosuvastatin	5-10	20-40

In patients unable to tolerate appropriate mod-hi dose statin according to their risk, use the highest tolerable statin dose as treatment option

Acronym List

AAA	abdominal aortic aneurysm
ABI	ankle brachial index
ACS	acute coronary syndrome
ASCVD	atherosclerotic cardiovascular disease
BAS	bile acid sequestrants
BID	twice a day
BP	blood pressure
CABG	coronary artery bypass graft
CAC	coronary artery calcium
CAD	coronary artery disease
CHF	chronic heart failure
CVA	cerebral vascular accident
CVD	cardiovascular disease
DM	diabetes mellitus
EF	ejection fraction
ESRD	end stage renal disease
HDL-C	high density lipoprotein cholesterol
IMT	intimal medial thickness
LDL-C	low density lipoprotein cholesterol
LE	life expectancy
LFT	liver function tests
MI	myocardial infarction
Mod-Hi	moderate to high
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PVD	peripheral vascular disease
QD	once a day
RF	risk factors
SDM	shared decision making
TC	total cholesterol
TG	triglycerides
TIA	transient ischemic attack
TLC	therapeutic lifestyle changes

Recommendations

Assessment of Cardiovascular Risk

A

1. We recommend CVD risk screening for men > age 35 and women > age 45, including a lipid profile and a risk calculation. [**Strong For**]
2. We recommend **against** routine screening for dyslipidemia outside of the context of a cardiovascular risk assessment. [**Strong Against**]

B.

- Patients with Severe Systolic Chronic Heart Failure (CHF), End Stage Renal Disease (ESRD) and on Dialysis, or a Limited Life Expectancy are excluded from this guideline

D.

3. For risk calculation, we suggest a 10-year risk calculator. [**Weak For**]

C.

4. We suggest that patients being considered for statin therapy be assessed for other CVD risk factors, including, but not be limited, to the following:

   a. Age (*males >35 and females >45*)

   b. Family history of premature coronary artery disease (CAD); definite myocardial infarction (MI) or sudden death before age 55 in father or other male first-degree relative, or before age 65 in mother or other female first-degree relative

   c. Current tobacco use/cigarette smoking (or within the last one month)

   d. Hypertension — *(systolic blood pressure [SBP] >140 mmHg or diastolic blood pressure [DBP] >90 mmHg confirmed on more than one occasion, or current therapy with anti-hypertensive medications)*

   e. Diabetes mellitus — *A diagnosis of DM is made if any of the following: a) Fasting plasma glucose (FPG) is ≥126 mg/dL on at least two occasions, or b) A single hemoglobin A1c (HbA1c) reading of ≥ 6.5%, confirmed with a FPG ≥126 mg/dL (these tests can be done on the same or different days); or c) HbA1c is ≥ 7% on two occasions using a clinical laboratory methodology standardized to the net splanchnic glucose production (NSGP) (not at the point of care); or d) Symptoms of hyperglycemia and a casual (random) glucose ≥ 200 mg/dL on two occasions. However, casual (random) plasma glucose is not recommended as a routine screening test. (see VA/DoD DM CPG at:* http://www.healthquality.va.gov/guidelines/CD/diabetes/DM2010_FUL-v4e.pdf)

   f. Level of HDL-C (Less than 40 mg/dL confirmed on more than one occasion)

   [Weak For]

   Modified from the 2006 CPG without an updated systematic review of the evidence. *

5. We suggest **against** the routine use of high-sensitivity C-reactive protein (hsCRP) testing. [**Weak Against**]
6. We suggest **against** the routine use of coronary artery calcium (CAC) testing. [**Weak Against**]

Pharmacotherapy for Primary Prevention (Patients without a history of ASCVD or ACS)

E, F

7. We suggest shared decision making regarding pharmacologic treatment for patients with an estimated 10-year CVD risk of 12% or greater that takes into consideration the known minimal harms and substantial benefits of moderate-dose therapy in this group of patients. [**Weak For**]
8. We suggest initiation of a moderate-dose statin for patients with an estimated 10-year CVD risk of 12% or greater. [**Weak For**]
9. We suggest considering a moderate-dose statin for patients with a 10-year CVD risk between 6% and 12% following a discussion of the known minimal harms, benefits derived from limited evidence, and an exploration of the patient's values and preferences. [**Weak For**]
10. For primary prevention, we recommend a moderate-dose statin as the agent of choice to reduce CVD risk if the patient chooses pharmacologic therapy. [**Strong For**]
11. For primary prevention in patients who are unable to tolerate statins, we suggest reinforcing adherence to positive lifestyle changes. For patients who prefer to try pharmacotherapy, we suggest considering treatment with gemfibrozil or bile acid sequestrants (BAS), noting that these agents have been associated with only a small CVD risk reduction and studied in limited populations, e.g., males with LDL-C >190 mg/dL. [**Weak For**]
12. We suggest establishing baseline liver function tests (LFTs) and creatinine kinase (CK) before initiation of drug therapy. [**Weak For**]
13. We recommend **against** routinely measuring LFTs or CK after a moderate-dose statin is initiated. [**Strong Against**]

Pharmacotherapy for Secondary Prevention (Patients with a history of ASCVD or ACS)

14. In patients with established ASCVD, we recommend use of a moderate-dose statin following a discussion of the minimal harms, substantial benefits, and an exploration of the patient's values and preferences. [**Strong For**]
15. In patients with ASCVD who are able to tolerate statins, we recommend **against** the routine use of non-statin lipid lowering drugs (e.g., fibrates, niacin, ezetimibe, omega-3 fatty acids, etc.) either alone as monotherapy or added to statins. [**Strong Against**]
16. In patients with ASCVD who are unable to tolerate statins, we suggest reinforcing adherence to positive lifestyle changes and suggest offering niacin or gemfibrozil, noting that these agents have been associated with only a small CVD risk reduction and studied in limited populations (e.g., males with low HDL-C). [**Weak For**]
17. We strongly recommend **against** the routine use of LDL–C and non-HDL–C goals for the secondary prevention of ASCVD. [**Strong Against**]
18. We suggest offering a high-dose statin only in select patient populations (e.g., ACS, multiple uncontrolled risk factors or recurrent CVD events on moderate-dose statin) following a discussion of the added harms, small additional benefits, and an exploration of the patient's values and preferences. [**Weak For**]

I.

19. We suggest measuring LFTs 4-12 weeks after the initiation of high-dose statin. [**Weak For**]

Non-pharmacological Approaches

H.

20. We recommend all adults adopt healthy lifestyles to reduce CVD risk, including: [**Strong For**]
    a. Tobacco cessation for all smokers (See VA/DoD Tobacco Use CPG 2008 at: http://www.healthquality.va.gov/guidelines/cd/mtu/index.asp)
    b. Therapeutic Lifestyle Changes (TLC) diet to optimize nutrition (For overweight and/or obese patients, see VA/DoD CPG for Management Of Overweight And Obesity 2014 at: http://www.healthquality.va.gov/guidelines/cd/obesity/index.asp)
    c. Optimal physical activity (See 2008 Physical Activity Guidelines for Americans, at http://www.health.gov/paguidelines/pdf/paguide.pdf)

    Modified from the 2006 CPG without an updated systematic review of the evidence. *

21. We suggest offering high-risk patients (see text for definition) a dietitian-monitored Mediterranean diet supplemented with either extra-virgin olive oil (roughly 1 liter per week) or 30g of mixed nuts per day (15g of walnuts, 7.5g of hazelnuts, and 7.5g of almonds) for the reduction of CVD events. [**Weak For**]
22. We suggest that each patient's diet be individualized based on a nutrition assessment (preferably by a RD), other CVD risk factors, other disease conditions, and patient's lifestyle. [**Weak For**]

    Modified from the 2006 CPG without an updated systematic review of the evidence. *

23. We recommend treating the common secondary causes of elevated TGs: dietary indiscretion (e.g., refined sugars), alcohol use, hypothyroidism, and hyperglycemia. [**Strong For]**

    Modified from the 2006 CPG without an updated systematic review of the evidence. *

24. We suggest for patients with TGs greater than 500 mg/dL a strict diet therapy including avoidance of alcohol, restriction of dietary fat, and avoidance of refined sugars. We suggest for patients with TGs greater than 1000 mg/dL a very low fat diet to reduce chylomicronemia and risk of acute pancreatitis. [**Weak For**]

Follow-up

G.

25. We suggest CVD risk assessment every five years for patients with low CVD risk and not on statin therapy. [**Weak For]**
26. We suggest CVD risk assessment every two years for patients with intermediate CVD risk or with appearance of a new CVD risk factor (e.g., new diagnosis of type 2 DM or hypertension) and not on statin therapy. [**Weak For**]

** These "modified" recommendations from the previous CPG published in 2006 were considered still relevant to health care providers and were carried forward into this CPG. For additional information please refer to the section Reconciling 2006 CPG Recommendations in the full CPG*

NOTES

Note: Refer to product prescribing insert for more information regarding use restrictions, dose modification, dosing in special populations (e.g., renal or liver impairment, advanced age, pregnancy, etc.), drug-drug interactions and adverse events.

Table 7 . Summary of Statin and Non-statin Pharmacologic Agents

Drug Category	Dose	Adverse Drug Events	Notes
Statins			
Atorvastatin	10-80 mg once daily (high dose = 40-80 mg) (moderate dose = 10-20 mg)	Statins are generally well tolerated. Myalgia, myopathy and rarely, rhabdomyolysis may occur. Risk of rhabdo is increased in the presence of interacting drugs, higher statin doses, renal or liver impairment, hypothyroidism, frailty, advanced age, etc. Other adverse events include diabetes, LFT elevation and possible non-serious, reversible cognitive effects including memory loss and confusion. However, an association between statins and an effect on cognition has not been confirmed.	First line therapy for primary or secondary prevention of ASCVD. Monotherapy with statins represents the best evidence for cardiovascular risk reduction.
Rosuvastatin	5-40 mg once daily (high dose = 20-40 mg) (moderate dose = 5- 10mg)		
Simvastatin	5-40 mg once daily (moderate dose = 20-40 mg)		
Lovastatin	20-80 mg once daily (moderate dose = 40 mg)		
Pravastatin	10-80 mg once daily (moderate dose = 40-80 mg)		
Fluvastatin	20-80 mg/day (moderate dose = 40 mg twice daily or 80 mg XR/day)		
Pitavastatin	1-4 mg once daily (moderate dose = 2-4 mg)		
Fibrates			
Fenofibrate	Nanocrystal 145 mg/day Micronized 43-200 mg/day Micronized taken with meals. Dose varies depending upon micronized product used.	Skin rash, gastrointestinal (nausea, bloating, dyspepsia, cramping), headache myalgia, myopathy, increased serum transaminases, elevation in serum creatinine, cholelithiasis, etc.	Combination with a statin in the ACCORD trial showed no evidence of improved patient outcomes beyond statin based therapy (Subgroup analysis showed potential harm in women and a potential benefit in those with high TG and low HDL-C). [6] Avoid in patients with CrCl < 30 ml/min, active liver disease including primary biliary cirrhosis, and preexisting gallbladder disease.
Fenofibric Acid	35-105 mg once daily Taken without regard to meals.	See Fenofibrate	Avoid in patients with CrCl < 30 ml/min, active liver disease including primary biliary cirrhosis, and preexisting gallbladder disease.
Gemfibrozil	600 mg twice daily Take 30-60 min before meals.	See Fenofibrate	VA-HIT (secondary prevention) gemfibrozil BID for 5 years vs. placebo in men with low HDL-C and moderately elevated LDL-C resulted in a significant reduction in nonfatal MI and death or cardiac origin. [7] Avoid in patients with CrCl < 30 ml/min, active liver disease including primary biliary cirrhosis, and preexisting gallbladder disease.

Table 7 . Summary of Statin and Non-statin Pharmacologic Agents			
Drug Category	**Dose**	**Adverse Drug Events**	**Notes**
Bile Acid Sequestrants (BAS)			
Cholestyramine	4-24 g/day Take within 30 min of a meal.	Nausea, bloating, cramping, and constipation; elevations in hepatic transaminases and alkaline phosphatase and increases in triglycerides.	Separate BAS from other medications by taking them at least 1 hour before BAS or at least 4-6 hours after BAS to avoid a reduced effect of other medications.
Colestipol	5-30 g/day		
Colesevelam	3.75 g/day Take with meals daily or divided twice daily.		Colesevelam has less drug interactions than do the older BAS; will not decrease vitamin A, D, E, K absorption as much.
Niacin Products			
Niaspan (ER Niacin)	500-2000 mg/day Initial: 500 mg at bedtime x 4 weeks, then 1 g at bedtime x 4 weeks; adjust dose to response and tolerance.	Flushing, edema, glucose intolerance, GI distress (abdominal pain, diarrhea, dyspepsia, nausea, vomiting), pruritus, GI bleeding, elevation of liver transaminases and hepatic toxicity.	Combination with a statin in AIM-HIGH and HPS2-THRIVE showed no evidence of improved patient outcomes beyond statin based therapy in patients with ASCVD with well controlled LDL-C. [8,9] An increased risk for serious adverse events was observed in HPS2-THRIVE in the niacin/laropiprant group. [8] The contribution of laropiprant to the increased risk for adverse events is unknown. Avoid in patients with active liver disease, active peptic ulcer disease, and arterial bleeding.
Niacor (IR Niacin)	250-6000 mg/day Initial: 250 mg daily with evening meal; increase frequency and/or dose every 4-7 days.		
Cholesterol Absorption Inhibitors			
Ezetimibe	10 mg/day		Unknown benefit for reducing cardiovascular risk in primary or secondary prevention.
Fish Oil			
Fish Oil	1-4 g/day, as single dose or divided twice daily.	Taste perversion, dyspepsia, pruritus, and rash; hepatic ALT and AST increased. May increase LDL- C.	Meta-Analysis by Rizos et al. (2012) included 60 studies enrolling 68,680 patients. Use of omega-3 fatty acids was not associated with a reduction in all- cause mortality, cardiac death, MI, stroke or sudden death. [10]

ALT= alanine transaminase; ASCVD= atherosclerotic cardiovascular disease; AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides Impact on Global Health Outcomes; AST= aspartate aminotransferase; LDL-C= low density lipoprotein cholesterol; BAS= bile acid sequestrants; BID= twice daily; CrCl= creatinine clearance; g= gram(s); HDL –C= high density lipoprotein cholesterol; HPS2-THRIVE= Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events; INR= international normalized ratio; IR= immediate release; mg= milligram(s); ULN= upper limit of normal; VA-HIT= Veterans Affairs High-Density Lipoprotein Intervention Trial

REFERENCES

1. American Heart Association. What is cardiovascular disease (heart disease)? 2011; http://www.heart.org/HEARTORG/Caregiver/Resources/WhatisCardiovascularDisease/What-is-Cardiovascular-Disease_UCM_301852_Article.jsp. Accessed July 8, 2014.
2. Department of Veterans Affairs and Department of Defense. Clinical practice guideline for the management of dyslipidemia. 2006; http://www.healthquality.va.gov/guidelines/CD/lipids/lip05_950_final2.pdf. Accessed December 1, 2014.
3. American Heart Association. What your cholesterol levels mean. 2014; http://www.heart.org/HEARTORG/Conditions/Cholesterol/AboutCholesterol/What-Your-Cholesterol-Levels-Mean_UCM_305562_Article.jsp. Accessed July 8, 2014.
4. Centers for Disease Control and Prevention (CDC). Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol-United States, 1999-2002 and 2005-200. MMWR Morb Mortal Wkly Rep. Feb 4 2011;60(4):109-114.
5. Lederle FA, Bloomfield HE. Drug treatment of asymptomatic hypertriglyceridemia to prevent pancreatitis: Where is the evidence? Ann Intern Med. Nov 6 2012;157(9):662-664.
6. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. Apr 29 2010;362(17):1563-1574.
7. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs high-density lipoprotein cholesterol intervention trial study group. N Engl J Med. Aug 5 1999;341(6):410-418.
8. Lavigne PM, Karas RH. The current state of niacin in cardiovascular disease prevention: A systematic review and meta-regression. J Am Coll Cardiol. Jan 29 2013;61(4):440-446.
9. Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. Jul 17 2014;371(3):203-212.
10. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: A systematic review and meta- analysis. JAMA. Sep 12 2012;308(10):1024-1033.

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