

# Adult Cholesterol Management

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## **Disclaimer**

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## Definitions

**Primary Prevention** refers to people without established coronary artery disease (CAD).

**Secondary Prevention** refers to people with established CAD.

**CAD “Risk Equivalents”** include the following:

- Cerebrovascular disease: atherosclerotic stroke or transient ischemic attack (TIA), or carotid artery obstruction of more than 50%.
- Peripheral arterial disease (PAD)
- Abdominal aortic aneurysm (AAA)
- Diabetes mellitus (DM), age 40 years or older
- A 10-year risk for coronary events of 25 % or more
- Chronic Kidney Disease (CKD) stages 4-5: National Kidney Foundation (NKF) Stages 4-5 defined as a Glomerular Filtration Rate (GFR) of 30 mL/min/1.73 m<sup>2</sup> or less, persisting for at least three months.

## Screening Recommendations (See Table 1)

### No CAD Risk Factors

#### Baseline

A total cholesterol (TC) + high-density lipoprotein cholesterol (HDL-C) test or fasting lipid panel (FLP) at age twenty.

*Consensus-based*

#### Follow-Up

- **Normal lipid levels** (TC less than 240 mg/dL, HDL-C 40 mg/dL or higher) and **no risk factors:** TC + HDL-C or FLP every five years beginning at age 35 for men and age 45 for women. *Evidence-based (A)*
- **New risk factor identified:** FLP recommended
- There is insufficient evidence to make a recommendation for or against follow-up cholesterol screening in men aged 20-34, or in women 20-44 years old, with normal baseline lipid levels. *Evidence-based (I)*

### CAD Risk Factors Present

#### Baseline

- FLP at age twenty. *Evidence-based (B)*

#### Follow-Up

FLP annually and any time a new risk factor is identified. *Consensus-based*

### Known CAD or CAD Risk Equivalents

An annual FLP is recommended *Consensus-based*

Refer to the “10-Year CAD Risk (%) and Recommendations for Dyslipidemia Drug Treatment Tables” for the 10-year risk.

Table 1: Recommendations for Lipid Screening and Testing				
	No Nonlipid CAD Risk Factors*		One or More Nonlipid Risk Factors*	
	Test	Frequency	Test	Frequency
<b>At Baseline</b>	TC + HDL-C** or FLP	Age 20	FLP	Age 20
<b>Follow-up</b>				
TC > 240 mg/dL <b>OR</b> HDL-C < 40 mg/dL	FLP	Annually	FLP	Annually
TC ≤ 240 mg/dL <b>AND</b> HDL-C ≥ 40 mg/dL	TC + HDL-C** FLP if new risk factor identified	Every 5 years starting at age 35 for men, 45 for women <b>AND</b> any time a new risk factor is identified	FLP	Annually <b>AND</b> any time a new risk factor is identified
<p>*<b>Nonlipid Risk Factors for CAD:</b> Family history of CAD, sudden death, PAD or cerebrovascular disease in a first-degree relative aged &lt;55 (men) and &lt;65 (women); DM; smoking; hypertension (BP &gt;140/90 mm Hg or taking BP medication).  **TC + HDL-C can be nonfasting.</p>				

## Primary Prevention

Use the “10-Year CAD Risk (%) and Recommendations for Dyslipidemia Drug Treatment Tables” to identify people appropriate for pharmacologic treatment. *Evidence-based (B)*

### LDL-C Goal less than 130 mg/dL

- All primary prevention patients
- Non-HDL-C less than 160 mg/dL is an optional goal after LDL-C is at goal.

### LDL-C Goal less than 100 mg/dL

- Patients with diabetes mellitus (DM) 40 years of age or older
  - 10-year risk of CAD of 25 percent or more
  - CKD Stages 4-5
- Non-HDL-C of less than 130 mg/dL is an optional goal after LDL-C is at goal (Non-HDL-C = TC minus HDL-C).

Use lifestyle modifications as first-line therapy; add simvastatin if LDL-C levels remain high (see “Drug Treatment Strategy” section).

## Risk Stratification and Treatment Goals

Lipid-lowering drugs are recommended for patients at high risk for CAD, but are less beneficial for patients at lower risk. Table 2 is a simplified treatment priority grid with goals.

Table 2. Adult Treatment Recommendations by Risk Factor						
Conditions	Very High Risk ACS CAD + DM CAD + MetSyn CAD + Smoking	CAD, DM, PAD, CVA, TIA CKD, AAA	Smoker or HTN <sup>1</sup>	0-1 Risk Factors <sup>2</sup>	CAD DM, PAD CVA, TIA CKD, AAA <sup>3</sup>	Anyone Without CAD Risk Equivalent
Treat with diet & drugs at:	Any LDL	Any LDL	LDL > 130	LDL > 130	TG > 400	TG > 500
To goal of:	LDL of 70-90 <sup>4</sup> Optional LDL-C goal < 70	LDL-C < 100 <sup>5</sup> Optional LDL-C goal < 80	LDL < 130 <sup>6</sup>	LDL < 130	TG < 200	TG < 400

Definitions: ACS – Acute Coronary Syndromes ( $\leq 3$  months); CAD – Coronary Artery Disease; DM – Diabetes Mellitus; Met Syn – Metabolic Syndrome; PAD – Peripheral Arterial Disease; CVA – Cerebrovascular Accident, TIA – Transient Ischemic Attack; CKD – Chronic Kidney Disease; AAA – Abdominal Aortic Aneurysm

1. The presence of CAD or CAD risk equivalent automatically places the patient in the higher than 20% risk category. If a patient has two or more risk factors, the Framingham scoring system may be used to determine the 10-year CAD risk and recommended intensity of therapy. (<http://www.nhlbi.nih.gov/guidelines/cholesterol/>)
  2. Consider a 3-6 month trial of therapeutic lifestyle changes (TLC) prior to starting drugs for these patients.
  3. **The primary aim of therapy is to achieve the target goal for LDL-C**
  4. **For people with established CAD, an LDL-C goal of less than 70 mg/dL is optional**
  5. **There is no evidence to support an LDL-C goal of less than 70 mg/dL in people without CAD, who are CAD risk equivalents. however, based on the balance of costs/harms vs. benefits the LDL-C goal of less than 80 mg/dL is optional.**
  6. If smoker **and** HTN **and** HDL less than 40mg/dL, consider an LDL-C goal of less than 100 mg/dL.
- More aggressive treatment is warranted: as the patient ages (male  $\geq 45$ , female  $\geq 55$ ); if the patient has a family history of early coronary artery disease in a first degree relative (male < 55 years of age, female < 65); if the patient is at very high risk (male < 45 or female < 55); and metabolic syndrome.

## Treatment Strategy

Reducing LDL-C is the primary focus of treatment. Only after the LDL-C is at goal should attention be turned to managing triglycerides (TG's) and HDL-C, except when TG's are 500 mg/dL or higher, (see "High TG Level" section). Consult the medication tables for drug selection and dosing information (see Table 2 and Table 3). Before initiating drug treatment, rule out and, if present, correct secondary causes of dyslipidemia such as poor glycemic control, hypothyroidism, renal and liver disease, or medications. The recommendations below apply to adults selected for pharmacologic treatment.

- Simvastatin is recommended as first-line drug therapy to prevent CAD events and lower LDL-C. *Evidence-based (A) for the use of statins; consensus-based for the use of simvastatin specifically*
- Initiate simvastatin at a dose sufficient to lower LDL-C to less than 130 mg/dL and by at least 30-40 percent. Consider initiating with simvastatin 40 mg daily if LDL-C is higher than 220. *Consensus-based*

- If the LDL-C is not lower than 130 mg/dL after 6-8 weeks, increase the dose of the statin, switch to a more potent statin, and/or use combination lipid lowering therapy (see [“Combination Therapy”](#) section) *Consensus-based*
- For people with CAD risk equivalents, the LDL-C goal is lower than 100 mg/dL. Treatment is recommended regardless of baseline LDL-C. Titrate therapy as described above. *Consensus-based*
- When the LDL-C goal is achieved, reassess LDL-C annually to ensure that the patient remains at goal; it is optional to repeat the lipid panel in 3-6 months. *Consensus-based*

## Secondary Prevention and CAD Risk Equivalents

- Lifestyle modifications are recommended in ALL secondary prevention and CAD Risk Equivalent people (see [“Lifestyle Modifications”](#) section).
- Drug Treatment Strategy (See [Figure 1](#))
- Because of its proven effectiveness in event reduction, safety and cost, simvastatin is the preferred first-line statin. *Consensus-based*
- Initiate statins at a dose sufficient to reduce LDL-C to less than 100 mg/dL and by at least 30-40%. *Evidence-based (B)*
- Treatment is recommended even if baseline LDL-C is less than 100 mg/dL. (based on evidence of benefit from the Heart Protection Study). *Evidence-based (B)*
- In people with established CAD, an LDL-C goal of less than 70 mg/dL is optional. *Consensus-based* Refer to [Figure 1 “Statin Management in Secondary Prevention”](#) for specific treatment strategy recommendations.
- After LDL-C goal is achieved, reassess LDL-C annually to ensure that the patient remains at goal; it is optional to repeat the lipid panel in 3-6 months. *Consensus-based*

As shown in [Figure 1](#), a more aggressive LDL-C goal of less than 70 mg/dL is now an option. One study ([PROVE-IT](#)) among patients with acute coronary syndrome (ACS) supports an LDL-C goal of less than 70 mg/dL, while another study ([TNT](#)) among patients with stable CAD supports an LDL-C goal of less than 80mg/dL. However based on the balance of costs/harms versus benefits, the LDL-C goal of less than 70 mg/dL is optional. Three other trials have shown improved outcomes in a variety of people with CAD when the LDL-C was lowered below 80 mg/dL ([MIRACL](#), [AVERT](#), [REVERSAL](#)).

**When to intensify treatment in people with an LDL-C less than 100 mg/dL should be a shared decision with the patient, taking into consideration factors such as overall CVD risk, TG status, HDL-C, non-HDL-C, medication tolerance, cost and patient preference.**

## Lipid Management at the Acute Atherosclerotic Event

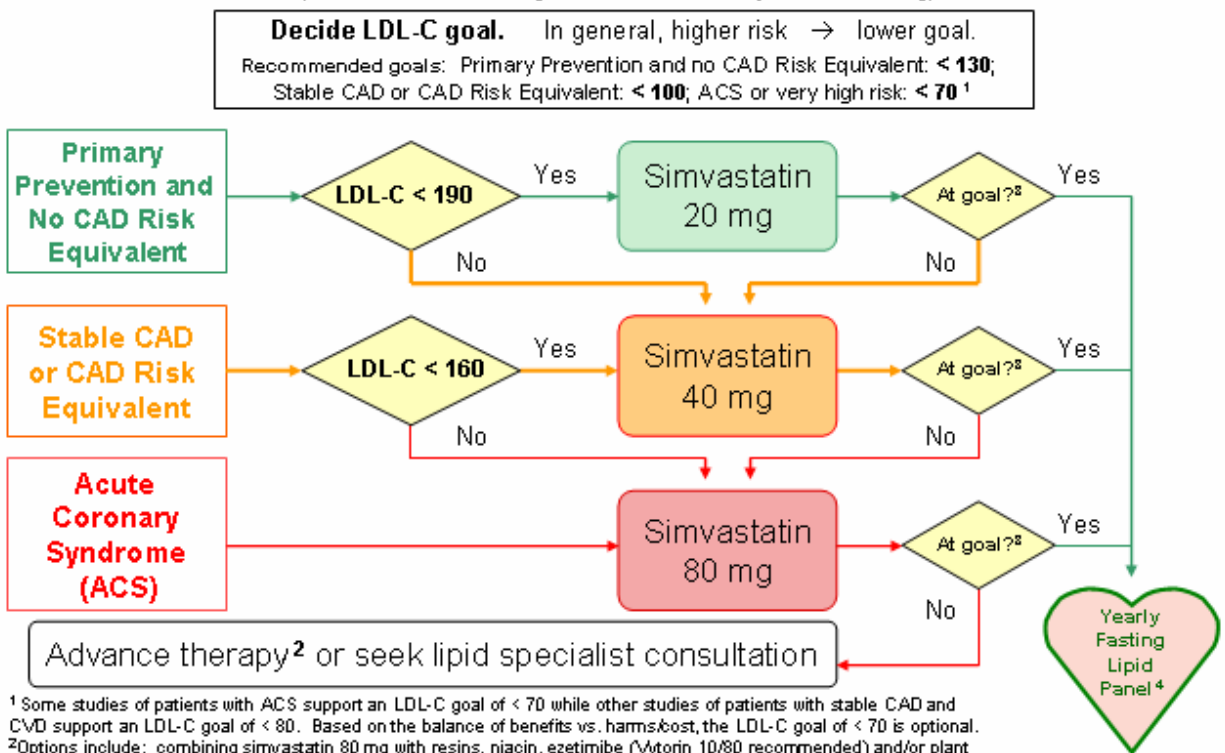
- Obtain a lipid panel and initiate lipid-lowering therapy as soon as possible but at least within 48 hours after hospital admission. Refer to [Figure 1](#) for specific treatment strategy recommendations. *Evidence-based (B)*
- Ensure that people receive a prescription for statin medication at discharge. *Consensus-based*
- Repeat the lipid panel two months after hospital discharge.
- Evidence shows that the stress of acute events can lower LDL-C levels for up to two to three months.
- Recent trial evidence suggests that people with ACS should receive aggressive statin lipid lowering treatment starting with simvastatin 80 mg daily. *Consensus-based*

- Emphasize the importance of lifestyle modifications and adherence to lipid-lowering medications.

## Aspirin Treatment

- Aspirin treatment (81-325 mg daily) is recommended for people who are at high enough risk to warrant statin treatment. *Consensus-based*
- Discuss aspirin treatment (81-325 mg daily) with people with a 10-year CAD risk of 10 percent or more who are not otherwise recommended for statin treatment. *Evidence-based (A)*  
(See [10-Year CAD Risk \(%\) and Recommendations for Dyslipidemia Drug Treatment Tables](#))

Figure 1. LDL Cholesterol-Lowering Strategy\*  
(LDL-C values are mg/dL; doses are daily in the evening)



<sup>1</sup> Some studies of patients with ACS support an LDL-C goal of < 70 while other studies of patients with stable CAD and CVD support an LDL-C goal of < 80. Based on the balance of benefits vs. harms/cost, the LDL-C goal of < 70 is optional.

<sup>2</sup>Options include: combining simvastatin 80 mg with resins, niacin, ezetimibe (Vytorin 10/80 recommended) and/or plant sterols/stanols; or switching to other statins (atorvastatin 80 mg [non-formulary] recommended)

<sup>3</sup>Re-evaluate LDL-C approximately 6 weeks after dose initiation or increase.

<sup>4</sup>Optional to check lipid panel at 3-6 months to be sure goal is maintained

Note: Consider lower initial statin dose in people with GFR <30 mL/min/1.73 m<sup>2</sup>. Dose can be cautiously increased if benefit exceeds risk.

\*For management of high triglycerides, see Table 2

## Lifestyle Modifications

- Strongly encourage
  - Tobacco cessation
  - Increased physical activity
  - A diet low in saturated fat
  - Increased intake of omega-3 fatty acids from fish, plant derived oils, or fish oil
  - A Mediterranean style diet

*Consensus-based for primary prevention; Evidence-based(B) for secondary prevention*

- There is currently insufficient evidence to recommend for or against low-carbohydrate diets for the prevention of atherosclerotic disease. *Consensus-based*
- Promoting alcohol consumption in people with or without atherosclerotic disease is NOT recommended because of the risk of developing alcohol-related problems. *Consensus-based*
- Evidence from observational studies has shown that smoking cessation, a moderate-to-high level of physical activity (e.g., 30 minutes of brisk walking five times per week), and a low-fat diet can reduce the risk of CAD. A Mediterranean diet emphasizes more bread, pasta, potatoes, fruit, vegetables, and fish, less meat, and replacement of butter and cream with olive or canola oil. Based on evidence obtained from secondary prevention studies, it is reasonable to assume that high fish oil and/or Mediterranean diets are also effective for primary prevention of atherosclerosis.
- For people who already drink alcohol, advise men to limit intake to two drinks a day, and women to one drink a day. (A drink is defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of liquor. *Consensus-based*)

## Special Considerations for Different Population Groups

### Metabolic Syndrome

Metabolic syndrome, also known as Insulin Resistance Syndrome, Syndrome ‘X’, or atherogenic dyslipidemia, is an important risk factor for CAD. The definition of metabolic syndrome has been adapted from the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) and is defined by the presence of three or more of the following in [Table 3](#) below:

Table 3. The Metabolic Syndrome Any Three or More of the Following	
RISK FACTOR	DEFINING LEVEL
Abdominal Obesity	Body Mass Index (BMI) > 30 kg/m <sup>2</sup> OR Waist circumference
Men	> 102 cm (> 40 in)
Women	> 88 cm (> 35 in)
TG	≥ 150 mg/dL
HDL	Men < 40 mg/dL
Women	< 50 mg/dL
Blood Pressure	>135 / >85 mmHg
Fasting Plasma Glucose*	100 – 125 mg/dL

\*An above normal Fasting Plasma Glucose (FPG) may imply insulin resistance; the American Diabetes Association (ADA) defines an FPG of less than 100 mg/dL as normal, the ATP III as less than 110 mg/dL).

While multiple risk factors may contribute to metabolic syndrome, it is beyond the scope of this guideline to recommend treatment for all the components. There is indirect evidence that the metabolic syndrome is associated with increased risk for CVD, but no data exist to quantify that risk beyond that calculated with the traditional risk factors. Similarly, there is no direct evidence informing whether people with metabolic syndrome should have lipid goals different than those determined by the traditional risk factors.

The treatment recommendations in this guideline focus on management of the lipid abnormalities associated with the metabolic syndrome. Reducing LDL-C is the primary treatment goal for all people with metabolic syndrome. An optional goal, after the LDL-C goal is achieved, is non-HDL cholesterol. There is evidence that statin treatment in people with DM and/or metabolic syndrome provides a large benefit.

Many of these patients may require combination therapy to achieve both LDL-C and non-HDL-C goals. See “[Lipid Risk Factors](#)” section and [Table 2](#) for specific goals and treatment recommendations. ATP III suggests that the presence of the metabolic syndrome in people with known CAD defines a “very high risk” and is a reason to consider the more aggressive LDL-C treatment goal of less than 70 mg/dL and the optional non-HDL-C goal of less than 100 mg/dL (see [Table 2](#) and [Figure 1](#)).

#### *Consensus-based*

Note: In people with diabetes mellitus, improving blood glucose control via therapeutic lifestyle changes and the appropriate use of glucose-lowering medications may make achieving non-HDL-C targets easier.

### **Diabetes Mellitus**

The Heart Protection Study showed that patients with diabetes are at high risk and derive a large benefit from primary prevention with statin treatment, regardless of baseline LDL-C. Based on this evidence, statin therapy, regardless of baseline LDL-C *Evidence-based (A)* and an LDL-C goal of less than 100 mg/dL is recommended by consensus for all patients with diabetes aged 40 years or older. *Consensus-based* In addition, patients with diabetes type I, from an early age on, are also at high risk for cardiac and vascular events and should be considered for statin therapy before the age of 40 years after 10-20 years of diabetes. Recently, with the epidemic of childhood obesity, the incidence of type II diabetes in adolescents and children is rising. Although there is no data about their risks of cardiac events as adults, it is presumed to be high, similar to patients with type I diabetes. *Consensus-based* Although the primary treatment is exercise, prudent diet and weight loss, consideration of statin therapy before the age of 40 years in these patients may be wise as well. In all pre-menopausal females prescribed statins, contraception and/or emergency contraception (levonorgestrel) should be discussed and prescribed.

### **Chronic Kidney Disease (CKD) Stages 4-5**

Patients with CKD, including NKF Stages 1, 2, and 3, are at increased risk for cardiovascular disease (CVD) morbidity and mortality. Because people with CKD frequently have other comorbidities, it is difficult to quantify the amount of CAD risk associated with CKD in the absence of comorbidities. There is insufficient evidence that patients with CKD Stages 1, 2 and 3, should be treated differently on the basis of their CKD status alone. There is evidence that people with CKD stages 4-5 are at sufficiently high risk to be considered a CAD Risk Equivalent. Therefore, treatment is recommended in patients with CKD stages 4-5 regardless of baseline LDL-C and the LDL-C goal is 100 mg/dL. See “[Medication Information](#)” section for dosing and safety recommendations for the use of lipid modifying drugs in CKD patients.

*Consensus-based*

### **Depression**

Depression makes it more difficult for patients to adopt healthy lifestyle changes and other self-care skills to manage their disease. Screen for depression, especially in the case of poor adherence to therapy.

#### **Ask these two questions to screen for depression:**

- During the past month, have you been bothered by feeling down, depressed, or hopeless?
- During the past month, have you often been bothered by little interest or pleasure in doing things?

If the patient answers “yes” to one or both of these questions, do a more careful diagnostic evaluation for depression. *Consensus-based*

### **Elderly Patients - Age 65 and Older**

Evidence from randomized controlled trials indicates that people between the ages of 65 and 82 years old benefit from lipid lowering. The effectiveness and benefits of drug therapy seen in this population are essentially the same as seen in people under the age of 65. The decision to treat should be based on a person’s lipid and nonlipid CAD risk factors and physiologic rather than chronologic age. *Evidence-based (A)* Very elderly people may have an increased risk for side effects from some lipid-lowering medications and reduced initial doses may be appropriate (see [Table 5](#)). *Consensus-based*

### **Men - 35 Years and Older**

Middle-aged men have a high prevalence of the major risk factors and are predisposed to abdominal obesity and the metabolic syndrome. *Consensus-based*

### **Young Adults - Men 20-35 Years - Women 20-45 Years Old**

Elevated serum cholesterol in young adults predicts a higher risk of premature CAD in middle age. Therefore, risk factor identification in young adults is an important factor in long-term prevention. *Consensus-based*

## Women - 45 Years and Older

Most CAD in women occurs after the age of 65 years old, generally 10-15 years later than in men. Women should be treated as aggressively as men. Multiple risk factors and the metabolic syndrome are seen as contributors to most premature CAD in women <65 years of age.

Clinical trials do not support the use of hormone therapy (HT) to reduce cardiovascular risk in post-menopausal women. Although HT may still be used for the treatment of menopausal symptoms, women who are taking estrogen, progesterone, or unopposed estrogen for cardiac protection are advised to discontinue treatment. *Consensus-based*

## Racial and Ethnic Groups

Risk factors confer a similar risk for all population groups and treatment strategies should apply to all ethnic groups. However, some risk factors are more common in certain ethnic groups, for example, hypertension in African-American patients, and diabetes in African-American, Hispanic-American and Native American peoples. *Consensus-based*

## Management of Specific Dyslipidemias

### Low HDL-C

HDL-C lower than 40 mg/dL is strongly associated with increased risk of CAD. The preponderance of evidence, however, continues to support LDL-C management as the first priority. If HDL-C remains low after LDL-C has been brought to goal, consider attempts to raise HDL-C. Options include tobacco cessation, increased physical activity, and medication. Niacin is the most potent HDL-C-raising agent, but fibrates and statins also increase HDL-C modestly. *Consensus-based*

### High HDL-C

The NCEP ATP III considers an HDL-C level of 60 mg/dL or more to be a “negative risk factor” that may counterbalance a positive risk factor. A high HDL-C level does not eliminate risk, however, and should not remove the focus from treating high LDL-C levels. Regardless of HDL-C level, treatment with statins is recommended for all people with CAD and CAD risk equivalents. *Consensus-based*

### Very High LDL-C

People with very high LDL-C (190 mg/dL or higher) are usually at high risk for CAD and treatment is recommended, regardless of other risk factors, unless there are compelling reasons against it. LDL-C lowering treatment is especially indicated in the presence of other risk factors, particularly a family history of premature CAD. *Consensus-based*

### Non-HDL-C (TC minus HDL-C)

The NCEP ATP III recommends using the non-HDL-C level as a secondary goal in people with TGs 200 - 499 mg/dL. The non-HDL-C goal is set at 30 mg/dL above the LDL-C goal. Weight reduction and physical activity are recommended; drug therapy to attain this goal could be considered in high-risk people once their LDL-C goal is reached. However, the primary aim of therapy in these people is to achieve the target goal for LDL-C. *Consensus-based*

### **High TG Level**

There is evidence that elevated TGs are independently associated with an increased risk of atherosclerosis. However, not all people with high TG's are at increased risk, and neither the threshold for initiation of therapy, nor the goal of therapy, is known. There is expert opinion that a desirable TG level is less than 150 mg/dL, but there are no studies to support the benefit of obtaining this level, or even of reducing TGs. Treatment decisions should be influenced by a person's other lipid levels and nonlipid CAD risk factors. Although there is no direct evidence, there is consensus that TG's 500 mg/dL or higher warrant treatment to prevent pancreatitis.

*Consensus-based*

**TABLE 4. Lipid Treatment Thresholds - Starting Medication Doses and Lipid Goals**

IF BASELINE LIPID LEVEL mg/dL is .....		STARTING MEDICATION AND DOSE IS...	LIPID GOAL IS LDL-C MG/DL	AFTER LDL-C IS AT GOAL - THE OPTIONAL LIPID GOAL IS... (mg/dL)
<b>Primary Prevention</b>				
People without DM, who are at sufficient CAD risk <sup>1</sup> to warrant lipid-lowering medications, including those with metabolic syndrome, but without CAD or CAD risk equivalents <sup>2</sup>	LDL-C $\geq$ 130 mg/dL	Simvastatin 20 mg qhs <sup>4</sup>	LDL-C < 130 mg/dL	
	TGs 200 - 499 mg/dL & LDL C < 130 mg/dL	It is optional to use fibrates and/or niacin and/or statins	LDL-C < 130 mg/dL	Non-HDL cholesterol < 160
	TG $\geq$ 500 mg/dL	Start with gemfibrozil 600 mg BID or niacin titrated to 1,000 mg BID. If the next LDL-C level is >130 mg/dL, switch to fenofibrate 160 mg daily w/ meal and ADD simvastatin 10 mg qhs. If higher doses are required to attain goal, consult a lipid specialist.		
	HDL-C < 40 mg/dL		Lifestyle modification	
<b>Secondary Prevention or CAD Risk Equivalents</b>				
All people with CAD, including those with metabolic syndrome and CAD, and/or CAD risk equivalents	LDL-C $\leq$ 160 mg/dL	simvastatin 40 mg qhs <sup>4</sup>	LDL-C < 100 mg/dL <sup>v</sup>	
	LDL-C > 160 mg/dL or 0	simvastatin 80 mg qhs	LDL-C < 100 mg/dL <sup>v</sup>	
	TGs 200 – 999 mg/dL and...			
	LDL-C $\leq$ 160 mg/dL	<b>Start with simvastatin 40mg</b> - if next LDL-C > 100 &/or TG > 500, increase to simvastatin 80 mg - if next TG > 500 consider reducing statin dose to 10 mg daily and adding fenofibrate or niacin	LDL-C < 100 mg/dL <sup>v</sup>	Non-HDL cholesterol < 130 mg/dL Optional goal: LDL-C < 70 mg/dL for patients with CAD Optional goal: LDL-C < 80 mg/dL for patients with CAD risk equivalents*** The primary aim of therapy is to achieve the target goal for LDL-C
	LDL-C > 160 mg/dL	<b>Start with simvastatin 80mg</b> - if next TG > 500 mg/dL consider reducing statin dose to 10 mg daily and adding fenofibrate or niacin		
	TG $\geq$ 1000 mg/dL	Start with simvastatin 10 mg daily AND fenofibrate 160 mg daily w/ meal or niacin titrated to 1,000 mg BID. If the next LDL-C level is >100 mg/dL, increase to simvastatin 20 mg if tolerated. If higher doses are required to attain goal, consult a lipid specialist.		
HDL-C < 40 mg/dL	Lifestyle modification; consider fibrates and/or niacin			
<b>Additional Dosing Instructions:</b> Lower initial doses of statins, fibrates and niacin should be considered in people with GFR <30 mL/min/1.73 m <sup>2</sup> , in medically complicated people, the very elderly, people taking interacting drugs and in combination lipid-modifying therapy because of the increased potential for myopathy. Statin doses can be cautiously increased, even up to maximal doses, if benefit exceeds risk. (See Table 5 for additional information.)				
<b>Additional Dosing Instructions:</b> <ul style="list-style-type: none"> <li>If baseline serum creatinine &gt; 1.5 mg/dL, start with half the recommended statin dose. If baseline serum creatinine &gt;3 mg/dL, consult a lipid specialist.</li> <li>All people taking statins should be warned about the risk and symptoms of rhabdomyolysis. Risk is increased in medically complicated people, the very elderly, people with compromised renal function, and interacting drugs. In these settings, lower statin doses and increased monitoring are recommended (see Table 5).</li> </ul> <ol style="list-style-type: none"> <li>Determine risk from the “10-Year CAD Risk (%) and Recommendations for Dyslipidemia Drug Treatment” tables</li> <li>People with CAD Risk Equivalents are those without known CAD, but with other known atherosclerosis (carotid artery disease [atherosclerotic stroke or TIA, or &gt;50 carotid artery obstruction], PAD, AAA), DM <math>\geq</math>40 years of age, a 10-year risk for coronary events <math>\geq</math>25%, or NKF CKD stages 3-5 (defined as GFR &lt;60 mL/min/1.73 m<sup>2</sup> persisting at least 3 months).</li> <li>There is no evidence to support LDL-C goal &lt;70 mg/dL in people without CAD, who are CAD risk equivalents. One study among patients with ACS supports an LDL-C goal of &lt;70 mg/dL, while another study among patients with stable CAD supports an LDL-C goal of &lt; 80mg/dL. However based on the balance of costs/harms vs. benefits the LDL-C goal of &lt;80 mg/dL is optional. [Optional non-HDL cholesterol goal &lt;100 mg/dL.]  <sup>v</sup>Clinical judgment is advised when considering lipid-lowering medications in adults with diabetes who are at very low 10-year CAD risk (&lt;7-10%).</li> <li>Titrate to consider advancing beyond simvastatin 80. Options include: other statins and/or combination with niacin, fibrates, resins, plant sterols/stanols, or ezetimibe depending on lipid profile, tolerance and cost. Consider lipid consultation until patient at goal</li> </ol>				

**MEDICATION INFORMATION** (See Table 5 for additional efficacy, safety and cost information.)

**STATINS**

**Statins** (simvastatin, lovastatin, others) are the most potent agents available for reduction of LDL-C and clinical events. They also moderately lower TG and raise HDL-C. Their effectiveness in lowering LDL-C and reducing clinical events, overall safety, tolerability, and ease of use make them the first-line drugs of choice for the management of dyslipidemia and CVD risk. Figure 1 and Table 2 provide recommended statin medications and starting doses for both primary and secondary prevention. For each doubling of the dose, an additional LDL-C reduction of approximately 6-7% is expected. If goal is not reached at maximum statin dose and potency, consider combination therapy or referral to a lipid specialist.

**Liver safety.** Multiple large, randomized controlled trials have found no difference in the rate of transaminase elevations between statin and placebo groups. This has been demonstrated even in children. Observational studies, which include unselected populations, have demonstrated that the incidence of significant transaminase elevations in people taking statins is small, generally in the range of 1-2%. When elevated transaminase levels do occur, they often resolve on rechallenge or even with continued therapy. The incidence of statin-induced true hepatotoxicity is so small that many authorities have questioned whether such an entity exists.

**It is important that patients recommended for statin therapy understand they are at far greater risk from cardiovascular disease than from statin-induced liver damage.** Nonetheless, it is prudent to not start a statin (or many other medications) in people who have active liver disease until disease stability is demonstrated. We therefore recommend obtaining an ALT prior to starting statin therapy. To be conservative, we also recommend an ALT test 6 weeks after treatment initiation and after each dosage increase. Stop the statin if the ALT increases to >3 times the upper limit of normal. See “Management Recommendations” below for next steps.

**Muscle symptoms.** Though infrequent, significant generalized muscle aches and/or weakness can occur in association with statin use. Rarely, this can progress to serious myopathy and rhabdomyolysis. Muscle symptoms and possibly even myopathy can occur in the absence of any elevation of the CK enzyme. Further, CK enzyme elevation can occur in the absence of muscle symptoms or damage and in asymptomatic people not on statins. We therefore do not recommend routine monitoring of CK, but rather counseling the patient to report significant generalized muscle symptoms.

**Management recommendations.** If a patient on a statin experiences either ALT > 3 times the upper limit of normal or significant generalized muscle aches and/or weakness, we recommend the following three possible management strategies. Which option is chosen should depend on the seriousness of the adverse event and is a matter of individual judgment.

- Discontinue the statin until the ALT elevation or muscle symptoms resolve and rechallenge with the same statin and dose. Often the patient tolerates this, implying the adverse event was not related to the statin.
- Discontinue the statin until the ALT elevation or muscle symptoms resolve and restart the same statin at a lower dose. If tolerated, titrate up as needed and tolerated.
- Discontinue the statin until the ALT elevation or muscle symptoms resolve and start a different statin. We recommend simvastatin and lovastatin initially based on effectiveness, tolerability and cost factors. Pravastatin is an alternative, recommended on the theoretical basis of its hydrophilicity and minimal interactions with CYP3A4 inhibitors.

If after achieving the highest tolerated statin dose and potency the patient’s LDL-C is still above goal, we recommend instituting combination therapy by adding resins, niacin or ezetimibe. (See “Combination Therapy” section below.)

**DOSING AND SAFETY RECOMMENDATIONS FOR PATIENTS WITH CKD**

A reduced initial simvastatin dose (5-10 mg) is suggested in patients with GFR <30 mL/min/1.73 m<sup>2</sup>. Statin doses can be cautiously increased, even up to maximal doses, if benefit exceeds risk. Gemfibrozil may be the preferred fibrate in CKD because it is not associated with the increase in serum creatinine seen with fenofibrate. Using half-dose gemfibrozil may be appropriate for GFR <30 mL/min/1.73 m<sup>2</sup>, but some dosing references have reported that no dosage adjustment is necessary. The dose of niacin should be halved in people with severe renal dysfunction. Patients with CKD have a significantly increased risk for the development of myositis and rhabdomyolysis with combination therapy (e.g., statin-fibrate, statin-niacin).

**FIBRATES**

**Fibrates** (gemfibrozil, fenofibrate) are recommended as first-line treatment for people with TG >500 mg/dL. They raise HDL-C modestly but have variable effects on LDL-C, sometimes increasing it. ALT should be monitored and dyspepsia is an occasional adverse effect. Clinical evidence from the VA-HIT study suggests that gemfibrozil provides benefit for secondary prevention people with a low HDL-C and low LDL-C. However, because of the preponderance of statin clinical trial data, statins are the first-line drug choice, even in people with low HDL-C and low LDL-C (unless TG ≥500).

**NICOTINIC ACID**

**Niacin** lowers LDL-C and TG and is the most potent agent available for raising HDL-C. It has been shown to reduce CVD events, especially in combination with a statin in people with high CVD risk and low HDL-C. Flushing and pruritus are common adverse effects that can be minimized by slow up-titration, taking with food and taking an aspirin 30 minutes before each dose. Additional adverse effects include hepatotoxicity, dyspepsia, stomach ulcers, and increased uric acid. Though worsening of glucose tolerance often accompanies niacin use, improved cardiovascular outcomes have been demonstrated in people with and without diabetes. Sustained-release niacin is generally better tolerated than immediate-

	<p>release preparations, and has been safely used in clinical trials at doses of up to 2 grams daily (e.g., OTC Slo-Niacin in HATS). Hepatotoxicity has been reported with the OTC sustained-release niacin products, especially at high doses (&gt; 2 grams) and when patients were converted from immediate-release to sustained-release niacin on a mg: mg basis. The maximum dose for sustained-release and extended-release formulations is 2 grams daily; immediate-release preparations may be titrated further to a maximum of 3 to 4.5 grams daily in divided doses.</p> <p>Patients should be instructed to report symptoms suggestive of liver toxicity (fatigue, nausea, anorexia). Liver transaminase levels and FBS should be monitored at baseline and periodically.</p>
<b>CHOLESTEROL ABSORPTION INHIBITORS</b>	<p><b>Ezetimibe</b> inhibits absorption of dietary and biliary cholesterol. It is dosed at 10 mg daily. Used as monotherapy, it reduces LDL-C approximately 18%. It lowers TG slightly and can raise HDL-C minimally. As with niacin and resins, it may be useful in people who need LDL-C lowering but cannot tolerate statins, and as add-on therapy in people who are taking statins at the maximum tolerated dose but need additional LDL-C reduction. The effects of ezetimibe on cardiovascular morbidity and mortality have not been evaluated. Because of their proven outcome and safety data, statins remain the first-line therapy for people who require LDL-C reduction.</p>
<b>BILE ACID SEQUESTRANTS</b>	<p><b>Resins</b> (colestipol, cholestyramine) are not systemically absorbed and are therefore safe to use in people with liver disease. They lower LDL-C, have minimal if any effect on HDL-C, and often raise TG. They are useful in combination therapy (see "Combination Therapy"), but should not be used in the presence of elevated TG. No laboratory monitoring (other than lipid profiles) is necessary. Adverse effects include marked constipation and bloating, dyspepsia, abdominal pain, and interference with absorption of many medications when administered simultaneously. Combining a resin with a psyllium seed preparation may reduce GI side effects and further reduce the LDL-C slightly.</p>
<b>FISH OIL SUPPLEMENTS</b>	<p><b>Fish Oil Supplements</b> at a dose of 4 grams/day have been shown to significantly reduce TGs but also raise LDL-C. When TGs are very high (&gt;500 mg/dL) the LDL-C increase may be substantial. The clinical significance of either effect is not known. There is conflicting evidence regarding the use of fish oil supplements for CVD prevention, where lower doses (1 gram/day) have been evaluated.</p>
<b>COMBINATION THERAPY</b>	
<b>STATIN PLUS NIACIN</b>	<p>This combination is attractive because of the favorable effects of nicotinic acid on atherogenic dyslipidemia. Combining the powerful LDL-C-lowering action of statins with the TG-lowering and HDL-C-raising actions of nicotinic acid offers the potential to correct most forms of complex dyslipidemias. However, niacin has a spectrum of adverse events associated with its use (see Nicotinic Acid section) and the combination of statin plus niacin may increase the risk of myopathy and hepatotoxicity. If adding niacin at a dose of &gt;1000 mg/day, consider lowering the statin dose (e.g., simvastatin 10-20 mg daily, lovastatin up to 40 mg daily). People should be cautioned to stop taking the drugs and promptly report the occurrence of any symptoms of myopathy.</p>
<b>STATIN PLUS RESIN</b>	<p>Adding a small-to-moderate dose of resin to a statin provides further LDL-C lowering without the concern of increasing the likelihood of serious adverse effects.</p>
<b>STATIN PLUS FIBRATE.</b>	<p>This combination is useful in people with combined hyperlipidemia (elevated LDL-C and TG) and/or the metabolic syndrome. These people are at high risk for an atherosclerotic event which often justifies the small, but significant increased risk of the serious adverse events of severe myopathy and rhabdomyolysis seen with this combination of drugs. Careful patient selection and lower statin doses are recommended. People should be cautioned to stop the drugs and promptly report the occurrence of any symptoms of myopathy. The overall safety and efficacy of this combination on CVD event outcomes have not been established.</p>
<b>STATIN PLUS EZETIMIBE</b>	<p>Ezetimibe-simvastatin is a combination tablet with doses of simvastatin ranging from 10 mg to 80 mg. It can provide marked LDL-C lowering (up to 60%), but its effect on CVD event outcomes has not been evaluated. Ezetimibe-simvastatin tablet is preferred over the combination of ezetimibe and any other statin because of powerful LDC reduction, cost and patient convenience.</p>

**TABLE 5. LIPID-LOWERING DRUGS: MEDICATION EFFICACY, SAFETY AND COST**

DRUGS AND DOSING	LDL-C EFFECTS	HDL-C EFFECTS	TG EFFECTS	COMMENTS
<b>HMG-CoA REDUCTASE INHIBITORS (STATINS)</b> THE FOUR STATINS LISTED HAVE GOOD CVD OUTCOME DATA AVAILABLE				
<p><b>SIMVASTATIN</b></p> <ul style="list-style-type: none"> <li>■ 10 mg daily</li> <li>■ 20 mg daily</li> <li>■ 40 mg daily</li> <li>■ 80 mg daily</li> </ul> <p><b>LOVASTATIN</b></p> <ul style="list-style-type: none"> <li>■ 10 mg daily</li> <li>■ 20 mg daily</li> <li>■ 40 mg daily</li> <li>■ 80 mg daily (2 x 40 mg tablets)</li> </ul> <p><b>PRAVASTATIN</b></p> <ul style="list-style-type: none"> <li>■ 10 mg daily</li> <li>■ 20 mg daily</li> <li>■ 40 mg daily</li> <li>■ 80 mg daily</li> </ul> <p><b>ATORVASTATIN</b></p> <ul style="list-style-type: none"> <li>■ 10 mg daily (use ½ 20 mg tablet)</li> <li>■ 20 mg daily (use ½ 40 mg tablet)</li> <li>■ 40 mg daily (use ½ 80 mg tablet)</li> <li>■ 80 mg daily</li> </ul>	<p>27%↓ 34%↓ 41%↓ 47%↓</p> <p>20%↓ 27%↓ 34%↓ 41%↓</p> <p>20%↓ 27%↓ 34%↓ 41%↓</p> <p>34%↓ 41%↓ 47%↓ 54%↓</p>	<p>5-15%↑  5-15%↑  5-15%↑  5-9%↑ 5-9%↑</p>	<p>7-30%↓  7-30%↓  7-30%↓  7-30%↓</p>	<ul style="list-style-type: none"> <li>■ <b>Indications: High LDL-C, CAD, CAD Risk Equivalent.</b></li> <li>■ Simvastatin is the preferred statin based on evidence of efficacy, safety and cost. For optimal LDL-C reduction, administer simvastatin daily in the evening. See Table 2 for initial doses and other treatment considerations.</li> <li>■ Triglyceride reductions as well as increases in HDL-C vary as a function of baseline TG and HDL-C levels and statin dose.</li> <li>■ Side effects include myalgia (&lt;3%), muscle cramps (&lt;1.5%), weakness (&lt;2%), headache (&lt;4%), constipation (&lt;5%), flatulence (&lt;5%), nausea (&lt;2%), abdominal pain/cramps (2-3%), and elevated serum transaminase. Monitor ALT 6 weeks after initiation of medication and dose increases.</li> <li>■ Myopathy and potentially fatal rhabdomyolysis are rare side effects. The risk is increased in frail or medically complicated people, the very elderly, people with impaired renal function, and in the presence of interacting drugs. Consider reduced dosages.</li> <li>■ In people with GFR &lt;30 mL/min/1.73 m<sup>2</sup>, initiate with simvastatin dose 5-10 mg daily in the evening. Statin doses can be cautiously increased, even up to maximal doses, if benefit exceeds risk.</li> <li>■ Use lower maximum statin daily doses in people taking cyclosporine, gemfibrozil or fenofibrate, verapamil, diltiazem, amiodarone or niacin (≥ 1 gram daily).</li> <li>■ Use of erythromycin, clarithromycin, azole antifungals (ketoconazole, itraconazole), nefazodone, protease inhibitors, other potent inhibitors of CYP 3A4 or large or regular consumption of grapefruit juice is not recommended with lovastatin, simvastatin, and atorvastatin. Pravastatin may be an appropriate alternative for people on chronic therapy with the above medications based on a theoretical decreased potential for drug interactions.</li> <li>■ <b>Contraindications: Pregnancy and lactation</b>, active liver disease or unexplained persistent elevations of serum transaminase levels. Note: Statins may be used in people with elevated serum transaminase levels (&lt;3 x ULN) due to fatty liver/nonalcoholic steatohepatitis (NASH).</li> </ul>
<b>NIACIN (NICOTINIC ACID)</b>				
<p><b>IMMEDIATE-RELEASE NIACIN</b></p> <ul style="list-style-type: none"> <li>■ Initial dose: 50-100 mg/day</li> <li>■ Titrate slowly to 1000-3000 mg daily (in divided doses)</li> </ul> <p><b>SUSTAINED-RELEASE NIACIN</b></p> <ul style="list-style-type: none"> <li>■ 500-2000 mg qHS or 500-1000 mg BID</li> </ul> <p><b>EXTENDED-RELEASE NIACIN</b></p> <ul style="list-style-type: none"> <li>■ 500-2000 mg qHS</li> </ul>	<p>5-25%↓</p>	<p>15-35%↑</p>	<p>20-50%↓</p>	<ul style="list-style-type: none"> <li>■ <b>Indications: High LDL-C, Low HDL-C, and/or High TG.</b></li> <li>■ Flushing, itching, tingling, headache, pruritus, and dyspepsia are common side effects that may limit adherence. Careful dosage titration is required to promote tolerance and adherence to therapy. Aspirin (162-325 mg) 30 minutes before each niacin dose can minimize flushing/itching. Taking immediate-release niacin with meals may also mitigate flushing.</li> <li>■ <b>The maximum daily dose of extended-release or sustained-release niacin is 2000 mg daily.</b> The starting dose of niacin should be halved in people with severe renal dysfunction.</li> <li>■ Liver function can be impaired and fatal hepatic failure has occurred; monitor AST/ALT, fasting blood sugar, and uric acid.</li> <li>■ <b>Contraindications:</b> Acute liver disease, active peptic ulcer disease, paroxysmal atrial fibrillation, poorly controlled diabetes, and gout.</li> </ul>

**TABLE 5. LIPID-LOWERING DRUGS: MEDICATION EFFICACY, SAFETY AND COST (CONTINUED)**

DRUGS AND DOSING	LDL-C EFFECTS	HDL-C EFFECTS	TG EFFECTS	COMMENTS
<b>FIBRIC ACID DERIVATIVES (FIBRATES)</b>				
<p><b>GEMFIBROZIL</b></p> <ul style="list-style-type: none"> <li>■ 600 mg BID AC</li> </ul> <p><b>FENOFIBRATE</b></p> <ul style="list-style-type: none"> <li>■ Microcoated Tablets 54, 160 mg</li> <li>■ Usual initial dose: 160 mg daily with meal</li> </ul>	No change or ↑ or ↓	5-35%↑	20-50%↓	<ul style="list-style-type: none"> <li>■ <b>Indications: High TG and/or low HDL-C.</b></li> <li>■ Side effects include dyspepsia, rashes, abnormal liver function and (rarely) hepatitis (monitor ALT), gallstones, myopathy and rhabdomyolysis. Rhabdomyolysis has been reported with both gemfibrozil and fenofibrate as monotherapy. Further data are needed to clearly define the overall efficacy and safety of fibrates when used in combination with statins.</li> <li>■ Cautious use of lower statin doses is recommended if combination therapy with a fibrate is required due to the increased risk of myopathy and rhabdomyolysis.</li> <li>■ Use lower fibrate doses if GFR &lt; 30 mL/min/1.73 m<sup>2</sup>.</li> <li>■ Compared to gemfibrozil, fenofibrate provides an additional 6-11% LDL-C reduction in Type IIa and IIb dyslipidemias; marked increases in LDL-C (up to 45%) may result when either fibrate is used to treat patients with very high TGs (&gt; 500 mg/dL). The clinical significance of the TG lowering and the LDL -C increase is not known.</li> <li>■ Unlike gemfibrozil, fenofibrate is less likely to interact with statins and may be preferred when combination therapy is required. Both fenofibrate and gemfibrozil can increase sensitivity to warfarin (monitor INR).</li> <li>■ <b>Contraindications:</b> Pre-existing gallbladder disease, hepatic dysfunction, or severe renal dysfunction.</li> </ul>
<b>BILE ACID SEQUESTRANTS</b>				
<p><b>COLESTIPOL</b></p> <ul style="list-style-type: none"> <li>■ Powder for suspension (scoop) or 1 gm Tablets</li> </ul> <p><b>CHOLESTYRAMINE</b></p> <ul style="list-style-type: none"> <li>■ Powder for suspension (scoop)                             <ul style="list-style-type: none"> <li>■ 1 scoop (= 4 tablets) per day</li> <li>■ 2 scoops (= 8 tablets) per day</li> <li>■ 3 scoops (= 12 tablets) per day</li> <li>■ 6 scoops (max dose) per day</li> </ul> </li> </ul>	16%↓ 23%↓ 28%↓ 33%↓	0%-5%↑	0%- 20%↑	<ul style="list-style-type: none"> <li>■ <b>Indications: High LDL-C.</b></li> <li>■ Bile acid sequestrants are most effectively used in combination with other agents when further LDL-C reduction is required. <b>Not recommended when baseline TG &gt; 200 mg/dL.</b> Bile acid sequestrants can increase TG levels significantly (e.g., 20%). Colestipol and cholestyramine may be given once daily or in divided doses.</li> <li>■ Bile acid sequestrants may interfere with the absorption of other oral medications (e.g., levothyroxine, statins, ezetimibe); therefore, <b>other medications should be taken one hour before or four hours after resins.</b> Use caution in people on digoxin, levothyroxine, or coumadin. May impair absorption of vitamins, including fat soluble vitamins (e.g., vitamin K).</li> <li>■ Side effects commonly include constipation, dyspepsia, abdominal pain, bloating, belching, diarrhea, and nausea.</li> <li>■ <b>Contraindications:</b> Complete biliary obstruction, bowel obstruction, hypertriglyceridemia, hypersensitivity to bile acid sequestering resins.</li> </ul>
<b>CHOLESTEROL ABSORPTION INHIBITORS</b>				
<p><b>EZETIMIBE</b></p> <ul style="list-style-type: none"> <li>■ 10 mg daily</li> </ul> <p><b>EZETIMIBE/SIMVASTATIN</b></p> <ul style="list-style-type: none"> <li>■ 10 mg/10 mg daily</li> <li>■ 10 mg/20 mg daily</li> <li>■ 10 mg/40 mg daily</li> <li>■ 10 mg/80 mg daily</li> </ul>	18-20% ↓  45%↓ 52%↓ 55%↓ 60%↓	0-5%↑  5-15%↑	5-10%↓  23-35%↓	<ul style="list-style-type: none"> <li>■ <b>Indications: High LDL-C.</b></li> <li>■ Ezetimibe offers an alternative agent in people who cannot tolerate statins and as add-on therapy in people on maximum tolerated dose of statins who require additional LDL-C reduction.</li> <li>■ Ezetimibe inhibits dietary and biliary cholesterol absorption at the intestinal wall via its effect on brush border transporter proteins.</li> <li>■ Side effects: May increase risk of AST/ALT elevation with combination vs. statin alone; in short-term clinical trials there was no excess of myopathy/rhabdomyolysis with combination vs. statin alone.</li> <li>■ <b>The long-term effects of ezetimibe on cardiovascular morbidity and mortality have not been established, nor has the long-term safety and efficacy profile of ezetimibe + low dose statin compared with a strategy of high dose statin alone.</b></li> </ul>

**TABLE 5. LIPID-LOWERING DRUGS: MEDICATION EFFICACY, SAFETY AND COST (CONTINUED)**

DRUGS AND DOSING	LDL-C EFFECTS	HDL-C EFFECTS	TG EFFECTS	COMMENTS
<b>FISH OILS, OMEGA-3-ACID ETHYL ESTERS</b>				
<p><b>FOR TRIGLYCERIDE <math>\geq</math> 500 mg/dL REDUCTION:</b></p> <ul style="list-style-type: none"> <li>■ <b>OMEGA-3-ACID ETHYL ESTERS 1 GRAM CAPSULE</b> (465 mg EPA + 375 mg DHA per capsule) – <b>4 caps/day</b></li> <li>■ Extra Strength Fish Oil (240 mg EPA + 200 mg DHA per capsule) – <b>OTC</b> – <b>8 caps/day</b></li> <li>■ Omega-3 Fish Oil/Vit E Soft Gels (180 mg EPA + 120 mg DHA + 5 IU Vit E) - <b>OTC</b> – <b>12 caps/day</b></li> </ul>	0 - 45% $\uparrow$	<b>No effect</b>	45% $\downarrow$	<ul style="list-style-type: none"> <li>■ <b>Indications:</b> <ul style="list-style-type: none"> <li>■ Very high Triglycerides (<math>\geq</math> 500 mg/dL) – 4 grams per day (EPA + DHA)</li> <li>■ High Triglycerides (200 – 499 mg/dL) – 2-4 grams per day (EPA + DHA)</li> <li>■ History of myocardial infarction or 2<sup>o</sup> Prevention – 1 gram per day (EPA + DHA)</li> </ul> </li> <li>■ In patients treated with 4 grams daily for very high TGs, there has been an <u>increase</u> in LDL-C of up to 45%. The clinical significance of both the decreased TG and the increased LDL-C is not known.</li> <li>■ Side effects: Potential bleeding risk at high doses; patients receiving both fish oil and antiplatelet/antithrombotic agents should be monitored for bleeding complications.</li> </ul>
<p><b>FOR POST-MI OR 2<sup>o</sup> Prevention:</b></p> <ul style="list-style-type: none"> <li>■ <b>OMEGA-3-ACID ETHYL ESTERS 1 GRAM CAPSULE</b> (465 mg EPA + 375 mg DHA per capsule) – <b>1 cap/day</b></li> <li>■ Extra Strength Fish Oil (240 mg EPA + 200 mg DHA per capsule) – <b>OTC</b> – <b>2 caps/day</b></li> <li>■ Omega-3 Fish Oil/Vit E Soft Gels (180 mg EPA + 120 mg DHA) – <b>OTC</b> – <b>3 caps/day</b></li> </ul>	No effect	No effect	No effect	

# **APPENDIX A**

## Appendix A - “10-Year CAD Risk (%) and Recommendations for Dyslipidemia Drug Treatment” Tables

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# 10-Year CAD Risk (%) and Recommendations for Dyslipidemia Drug Treatment

## (For People WITHOUT Known Atherosclerosis or Chronic Kidney Disease Stages 4-5<sup>1</sup>)

Revised 12/06

<ul style="list-style-type: none"> <li>Select the table matching the person's gender.</li> <li>Find the column corresponding to the person's age, TC level, and HDL-C level.</li> <li>Find the row that matches the person's non-lipid risk factors, e.g., NONE, Hypertension (HTN), Diabetes (DM), Tobacco (TBCO).</li> <li>The number in the intersecting "cell" is the person's estimated risk (%) of a CAD event in the next 10 years.</li> <li>The color in the "cell" indicates the drug treatment recommendation and goals.</li> <li>CAD risk is estimated using TC and HDL-C. However, treatment thresholds and goals are based on LDL-C and non-HDL cholesterol. Non-HDL cholesterol = TC minus HDL-C.</li> </ul>	<ul style="list-style-type: none"> <li>Treatment <b>STRONGLY</b> recommended when 10-year CAD risk <math>\geq 25\%</math>, regardless of baseline LDL-C<sup>2</sup></li> <li>Treatment recommended for people with <b>DIABETES</b> <math>\geq 40</math> years old, regardless of baseline LDL-C<sup>2</sup></li> <li>Treatment <b>RECOMMENDED</b> if baseline LDL-C <math>\geq 130</math> mg/dL</li> <li>Treatment recommended if positive FhX of early atherosclerosis and baseline LDL-C <math>\geq 130</math> mg/dL<sup>3</sup></li> <li>Drug Treatment <b>NOT</b> recommended</li> </ul>	<ul style="list-style-type: none"> <li>Use statin treatment, regardless of baseline LDL-C.</li> <li>The goal is LDL-C <math>&lt; 100</math> mg/dL. After LDL-C is at goal, an optional goal is non-HDL cholesterol <math>&lt; 130</math> mg/dL.</li> <li>The goal is LDL-C <math>&lt; 130</math> mg/dL. After LDL-C is at goal, an optional goal is non-HDL cholesterol <math>&lt; 160</math> mg/dL.</li> </ul>
<p><b>*Treatment is recommended for all people with LDL-C <math>\geq 190</math> mg/dL, regardless of CAD risk.</b></p> <p><b>Aspirin treatment, 81-325 mg daily, is recommended for people who are at high enough risk to warrant statin treatment.</b></p> <p><b>Discuss aspirin treatment with people with 10-year CAD risk <math>\geq 10\%</math> who are not otherwise recommended for statin treatment.</b></p>		

### MEN

AGE:	30-34												35-39												40-44																							
TC:	160-199				200-239				240-279				280-319				160-199				200-239				240-279				280-319																			
HDL-C:	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39												
No Risk Factors	<1	<1	1	3	<1	1	2	4	1	2	2	5	1	2	3	6	<1	1	2	4	1	2	3	6	2	3	4	7	2	4	5	9	2	2	3	6	2	3	5	8	3	4	6	11	4	6	7	13
Hypertension (HTN)	1	2	2	5	2	2	3	7	2	3	5	8	3	4	6	10	2	3	4	7	3	4	6	10	4	5	7	12	5	7	9	14	3	4	6	11	4	6	8	13	5	8	10	16	7	9	12	19
Diabetes (DM) <sup>2</sup>	<1	1	2	4	1	2	3	5	2	3	4	7	2	3	5	9	1	2	3	6	2	3	5	8	3	4	6	10	4	5	7	12	2	4	5	9	3	5	7	12	4	6	9	14	6	8	10	17
Tobacco (TBCO)	1	2	3	5	2	3	4	7	2	3	5	8	3	4	6	10	2	3	4	8	3	4	6	10	4	5	7	12	5	7	9	15	3	5	6	11	4	6	8	14	6	8	10	16	7	10	12	19
HTN + DM <sup>2</sup>	2	3	4	7	2	4	5	9	3	5	7	11	4	6	8	13	3	4	6	10	4	6	8	13	5	8	10	16	7	9	12	18	4	6	9	14	6	9	11	18	8	11	13	21	9	13	16	24
TBCO + HTN	2	3	5	8	3	5	6	11	4	6	8	13	5	7	10	16	4	5	7	12	5	7	10	15	7	9	12	18	8	11	14	21	6	8	10	16	7	10	13	20	9	13	16	24	11	15	18	27
TBCO + DM <sup>2</sup>	2	3	4	7	3	4	5	9	3	5	7	12	4	6	8	14	3	4	6	11	4	6	8	14	5	8	10	16	7	9	12	19	5	7	9	14	6	9	11	18	8	11	14	21	10	13	16	24
HTN + DM <sup>2</sup> + TBCO	3	5	7	12	5	7	9	15	6	9	11	18	7	10	13	20	5	8	10	16	7	10	13	20	9	12	16	23	11	15	18	26	8	11	14	21	10	14	17	25	13	17	20	29	15	19	23	32

AGE:	45-49												50-54												55-59																							
TC:	160-199				200-239				240-279				280-319				160-199				200-239				240-279				280-319																			
HDL-C:	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39								
No Risk Factors	2	4	5	9	3	5	7	11	4	6	8	14	5	8	10	16	3	5	7	11	5	7	9	15	6	8	11	17	7	10	13	20	5	7	9	14	6	9	11	18	8	11	14	21	9	13	16	24
Hypertension (HTN)	4	6	8	14	6	8	11	17	8	10	13	20	9	12	16	23	6	8	11	17	8	11	14	21	10	13	17	25	12	16	19	28	8	11	14	21	10	14	17	25	13	16	20	29	15	19	23	32
Diabetes (DM) <sup>2</sup>	4	5	7	12	5	7	9	15	6	9	11	18	8	11	14	21	5	7	9	15	7	9	12	19	8	12	15	22	10	14	17	25	7	9	12	19	9	12	15	23	11	14	18	26	13	17	21	29
Tobacco (TBCO)	4	6	9	14	6	9	11	18	8	11	14	21	9	13	16	24	6	9	11	18	8	11	14	22	10	14	17	25	12	16	20	28	8	11	14	21	10	14	17	26	13	17	21	29	15	19	23	33
HTN + DM <sup>2</sup>	6	9	11	18	8	11	14	22	10	14	17	26	12	16	20	29	8	12	15	22	11	15	18	26	13	17	21	30	16	20	24	34	11	14	18	26	14	18	22	31	16	21	25	35	19	24	28	38
TBCO + HTN	8	11	14	21	10	14	17	25	12	16	20	29	15	19	23	32	10	14	17	25	13	17	21	30	16	20	24	34	18	23	27	37	13	17	21	29	16	21	25	34	19	24	28	38	22	27	32	42
TBCO + DM <sup>2</sup>	7	9	12	18	9	12	15	22	11	14	18	26	13	17	20	29	9	12	15	22	11	15	18	27	14	18	22	31	16	21	25	34	11	15	18	27	14	18	22	31	17	21	26	35	20	24	29	39
HTN + DM <sup>2</sup> + TBCO	11	14	18	26	14	18	22	30	16	21	25	34	19	24	28	38	14	18	22	31	17	22	26	35	20	25	30	39	23	28	33	43	17	21	26	35	21	26	30	40	24	29	34	44	27	33	38	48

AGE:	60-64												65-69												70-74																							
TC:	160-199				200-239				240-279				280-319				160-199				200-239				240-279				280-319																			
HDL-C:	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39	60-79	50-59	40-49	20-39				
No Risk Factors	6	8	11	17	8	11	14	21	10	13	17	25	12	16	19	28	7	10	13	20	10	13	16	24	12	16	19	28	14	18	22	31	9	12	15	23	12	15	19	28	14	18	22	31	17	21	25	35
Hypertension (HTN)	10	13	17	24	13	17	20	29	15	20	24	33	18	22	27	36	12	16	19	28	15	19	24	33	18	23	27	37	21	26	30	40	14	18	22	31	16	22	27	36	21	26	31	40	24	29	34	44
Diabetes (DM) <sup>2</sup>	8	11	14	22	11	14	18	26	13	17	21	30	16	20	24	33	10	14	17	25	13	17	21	30	16	20	24	34	18	23	28	37	12	16	20	29	16	20	24	33	19	23	28	37	21	26	31	41
Tobacco (TBCO)	10	14	17	25	13	17	21	29	16	20	24	33	18	23	27	37	12	16	20	28	15	20	24	33	18	23	28	37	21	26	31	41	15	19	23	32	18	23	27	37	21	26	31	41	24	30	34	44
HTN + DM <sup>2</sup>	13	17	21	30	17	21	25	35	20	25	29	39	23	28	32	42	16	20	24	34	20	24	29	39	23	28	33	43	26	31	36	46	18	23	28	37	22	28	32	42	26	32	36	46	29	35	40	50
TBCO + HTN	16	20	24	33	19	24	29	38	22	28	32	42	26	31	36	46	18	23	28	37	22	28	32	42	26	31	36	46	29	35	40	50	21	26	31	41	25	31	36	46	29	35	40	50	33	38	43	53
TBCO + DM <sup>2</sup>	14	18	22	30	17	22	26	35	20	25	30	39	23	28	33	43	16	21	25	34	20	25	29	39	23	29	33	43	26	32	37	47	19	24	28	38	23	28	33	43	26	32	37	47	30	35	40	50
HTN + DM <sup>2</sup> + TBCO	20	25	30	39	24	30	34	44	28	33	38	48	31	37	42	52	23	29	33	43	28	33	38	48	31	37	42	52	35	41	46	55	26	32	37	47	31	37	42	52	35	41	46	55	39	44	49	59





## APPENDIX B

### Appendix B – Evidence Grading Scheme Summary

Table 1: Label and Language of Recommendations\*

Evidence-Based Recommendations	
<p><b>Label:</b> <b>Evidence-based (A)</b></p>	<p><b>Language <sup>a</sup>:</b> The intervention is strongly recommended for eligible patients.</p> <p><b>Evidence:</b> The intervention improves important health outcomes, based on good evidence, and the Guideline Development Team (GDT) concludes that benefits substantially outweigh harms and costs.</p> <p>Evidence Grade: Good.</p>
<p><b>Label:</b> <b>Evidence-based (B)</b></p>	<p><b>Language <sup>a</sup>:</b> The intervention is recommended for eligible patients.</p> <p><b>Evidence:</b> The intervention improves important health outcomes, based on 1) good evidence that benefits outweigh harms and costs; or 2) fair evidence that benefits substantially outweigh harms and costs.</p> <p>Evidence Grade: Good or Fair.</p>
<p><b>Label:</b> <b>Evidence-based (C)</b></p>	<p><b>Language <sup>a</sup>:</b> No recommendation for or against routine provision of the intervention. (At the discretion of the GDT, the recommendation may use the language “option,” but must list all the equivalent options.)</p> <p><b>Evidence:</b> Evidence is sufficient to determine the benefits, harms, and costs of an intervention, and there is at least fair evidence that the intervention improves important health outcomes. But the GDT concludes that the balance of the benefits, harms, and costs is too close to justify a general recommendation.</p> <p>Evidence Grade: Good or Fair.</p>
<p><b>Label:</b> <b>Evidence-based (D)</b></p>	<p><b>Language <sup>a</sup>:</b> Recommendation against routinely providing the intervention to eligible patients.</p> <p><b>Evidence:</b> The GDT found at least fair evidence that the intervention is ineffective, or that harms or costs outweigh benefits.</p> <p>Evidence Grade: Good or Fair.</p>
<p><b>Label:</b> <b>Evidence-based (I)</b></p>	<p><b>Language <sup>a</sup>:</b> The evidence is insufficient to recommend for or against routinely providing the intervention. (At the discretion of the GDT, the recommendation may use the language “option,” but must list all the equivalent options.)</p> <p><b>Evidence:</b> Evidence that the intervention is effective is lacking, of poor quality, or conflicting and the balance of benefits, harms, and costs cannot be determined.</p> <p>Evidence Grade: Insufficient.</p>

Consensus-Based Recommendations	
<b>Label:</b>  <b>Consensus-based</b>	<p><b>Language <sup>a</sup>:</b> The language of the recommendation is at the discretion of the GDT, subject to approval by the National Guideline Directors.</p> <p><b>Evidence:</b> The level of evidence is assumed to be “Insufficient” unless otherwise stated. However, do not use the A, B, C, D, I labels which are only intended to be used for evidence-based recommendations.</p> <p>Evidence Grade: Insufficient, unless otherwise stated.</p>
<p>For the rare consensus-based recommendations which have “Good” or “Fair” evidence, the evidence must support a different recommendation, because if the evidence were good or fair, the recommendation would usually be evidence-based. In this kind of consensus-based recommendation, the evidence grade should point this out, e.g., “Evidence Grade: Good, supporting a different recommendation.”</p>	

<sup>[a]</sup> All statements specify the population for which the recommendation is intended.

\* Recommendations should be labeled and given an evidence grade. The evidence grade should appear in the rationale. Evidence is graded with respect to the degree it supports the specific clinical recommendation. For example, there may be good evidence that Drugs 1 and 2 are effective for Condition A, but no evidence that Drug 1 is more effective than Drug 2. If the recommendation is to use either Drug 1 or 2, the evidence is good. If the recommendation is to use Drug 1 in preference to Drug 2, the evidence is insufficient.