

Introduction

The following evidence-based guideline is intended to assist primary care physicians and other health care professionals in the management of dyslipidemia for primary and secondary prevention of atherosclerotic disease.

Definitions

Primary Prevention	Refers to people without coronary artery disease (CAD)
Secondary Prevention	Refers to people with established CAD
CAD Risk Equivalents	Refers to any of the following: <ul style="list-style-type: none"> ▶ Ischemic stroke/TIA, carotid artery stenosis (>50%), peripheral artery disease (PAD), abdominal aortic aneurysm (AAA) ▶ Diabetes mellitus and age 40 or older ▶ 10-year risk of coronary events >20%* ▶ Chronic kidney disease stages 4 or 5
Chronic Kidney Disease (CKD) Stages 4 and 5	National Kidney Foundation (NKF) Stages 4 and 5 are defined as a Glomerular Filtration Rate (GFR) <30 mL/min/1.73 m ² for at least 3 months

* Refer to the 10-Year CAD Risk tables: <http://cl.kp.org/pkc/nw/cpg/cpgs/support/dyslipidemia/risks.html>

Detection and Evaluation

1 CAD Risk Factors

- ◆ **Age:** Male 45 or older; Female 55 or older
- ◆ **Dyslipidemia:** Total cholesterol (TC) ≥200 mg/dL or low-density lipoprotein cholesterol (LDL-C) ≥100 mg/dL in secondary prevention or CAD risk equivalent population; or TC ≥240 mg/dL or LDL-C ≥130 mg/dL in primary prevention; or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL; or triglycerides (TG) ≥150 mg/dL.
- ◆ **Diabetes Mellitus**
- ◆ **Hypertension:** BP ≥140/90 mmHg or on antihypertensive medication
- ◆ **Current cigarette smoking**
- ◆ **Family history of premature CAD:** Clinical CAD or sudden death in a first-degree relative age 54 or younger for men or age 64 or younger for women

2 Lipid Screening, Testing and Monitoring

- ◆ See **Table 1** for Recommendations.
- ◆ Rule out and, if present, correct any secondary causes of dyslipidemia such as poor glycemic control, hypothyroidism, renal and liver disease, or medications.

3 Using 10-Year CAD Risk Tables to Determine Treatment Initiation Plan

The need for and intensity of treatment for dyslipidemia among primary prevention people depends on a person's overall risk for CAD. For primary prevention, use the **10-Year CAD Risk** tables to identify people appropriate for pharmacologic treatment: <http://cl.kp.org/pkc/nw/cpg/cpgs/support/dyslipidemia/risks.html>

The **10-Year CAD Risk** tables, based on the ATP III version of the Framingham risk model, estimate an individual's risk of a primary cardiac event. The number in each cell is the person's estimated risk (%) of a CAD event in the next 10 years. Risk status is based on No Tobacco (TBCO), TBCO, No blood pressure (BP)

Detection and Evaluation

(continued)

Meds, BP Meds, age, sex, SBP levels, TC and HDL-C levels, and non-lipid CAD risk factors. The **10-Year CAD Risk** tables recommend pharmacologic treatment for three different levels of risk:

RISK LEVEL	RECOMMENDATIONS FOR DRUG TREATMENT
HIGH: 20-48 %	Treatment STRONGLY RECOMMENDED when 10-year CAD risk > 20% if baseline LDL-C \geq 100 mg/dL
MEDIUM: 10-20 %	Treatment RECOMMENDED if baseline LDL-C \geq 130 mg/dL
LOW: 5-10 %	Treatment RECOMMENDED IF positive FHx of premature CAD AND baseline LDL-C \geq 130 mg/dL
VERY LOW: 0-5 %	Drug Treatment NOT RECOMMENDED

For men age 50 or older and women age 60 or older, it is **OPTIONAL** to measure hsCRP, and if hsCRP \geq 2 mg/L on 2 tests, treat with simvastatin 40 mg daily. The absolute benefit or cost effectiveness of using hsCRP to select patients for lipid-lowering treatment is not known. (See **Table 2** and **Section 4** below for recommendations on the appropriate use of the hsCRP test.)

TABLE 1: Recommendation for Lipid Screening, Testing and Monitoring

	TEST	AGE TO INITIATE SCREENING	FREQUENCY
No CAD Risk Factors	TC + HDL-C* OR Fasting Lipid Panel	Age 20 OR First KP visit	Every 5 years starting at age 35 for men, age 45 for women AND any time a new risk factor is identified
One or more CAD Risk Factors OR Known CAD OR CAD Risk Equivalents	Fasting Lipid Panel	When CAD, CAD Risk Equivalency OR CAD Risk Factor is identified	Annually

NOTE: An FLP should be done anytime a new risk factor is identified and approximately 6 weeks after medication initiation or adjustment.

* TC + HDL-C can be non-fasting.

** There is insufficient evidence to recommend for or against follow-up lipid screening in men age 20-34 or in women 20-44 with normal baseline lipid levels.

Adult Cholesterol Management

TABLE 2: LDL-C Treatment Recommendations

PEOPLE WITH:	BASELINE LDL-C (mg/dl)	LIFESTYLE MODIFICATIONS ARE RECOMMENDED IN ALL PATIENTS Initiate treatment with a daily evening dose of:	TARGET LDL-C (mg/dl)	SEE CORRESPONDING NUMBER IN TEXT	
Acute Coronary Syndrome	Any	Simvastatin 80 mg	<100 OPTIONAL <70 ¹	7 8 9	
◆ CAD or Ischemic Stroke/TIA	≥160	Simvastatin 80 mg	<100 OPTIONAL <70 ¹	7 8 10C	
◆ Diabetes Mellitus (DM) age ≥40	<160	Simvastatin 40 mg			
◆ AAA or PAD					
◆ Carotid artery stenosis (>50%)					
◆ Framingham 10-year risk ² >20%	≥160	Simvastatin 80 mg	<100	4 7 8 10D	
◆ DM age <40 WITH ≥1 risk factors ¹	100–159	Simvastatin 40 mg			
	<100	Simvastatin 40 mg OPTIONAL For Framingham 10-year risk ² >20%, hsCRP ⁵ also OPTIONAL			
DM Age <40 WITHOUT risk factors ⁴	≥160	Simvastatin 80 mg	<100	7 8 10D	
	130–159	Simvastatin 40 mg			
	<130	Simvastatin 40 mg OPTIONAL			
CKD Stage 4 or 5 (GFR < 30 mL/min/1.73 m ²)	≥100	Simvastatin 20 mg	<100	10E	
	<100	Simvastatin 20 mg OPTIONAL			
Framingham 10-year risk ² 10–20%	≥220	Simvastatin 80 mg	<130	3 4 6 8	
	130–219	Simvastatin 40 mg			
	<130	hsCRP ⁵ OPTIONAL			
Framingham 10-year risk ² <10%	≥220	Simvastatin 80 mg	<130	3 4 6 8	
	190–219	Simvastatin 40 mg			
	160–189	▶ WITH FHx of premature CAD ³ AND Framington 10-year risk ² 5-9%			Simvastatin 40mg
		▶ WITH FHx of premature CAD ³ AND Framington 10-year risk ² < 5%			Simvastatin 40 mg OPTIONAL
		▶ OR WITHOUT FHx of premature CAD ³			OR hsCRP ⁵ OPTIONAL
	130–159	▶ WITH FHx of premature CAD ³ AND Framington 10-year risk ² 5-9%			Simvastatin 40mg
		▶ WITH FHx of premature CAD ³ AND Framington 10-year risk ² < 5%			hsCRP ⁵ OPTIONAL
		▶ OR WITHOUT FHx of premature CAD ³			
	<130	hsCRP ⁵ OPTIONAL			

1. Based on the balance of benefits versus costs and harms, the LDL-C goal of <70 mg/dL is **OPTIONAL**.
2. Determine risk from the **10-Year CAD Risk** tables at <http://cl.kp.org/pkc/nw/cpg/cpgs/support/dyslipidemia/risks.html>
3. FHx of premature CAD = Family history of premature CAD = Clinical CAD or sudden death in a first-degree relative aged < 55 (men) or < 65 (women).
4. Risk factors are: Duration of DM ≥ 10 years, HTN, HDL-C < 40, FHx of premature CAD, or currently smoking.
5. hsCRP = It is **OPTIONAL** to measure hsCRP in men ≥ 50 and women ≥ 60 years old, and if hsCRP ≥ 2 mg/L on 2 tests, treat with simvastatin 40 mg. The absolute benefit or cost effectiveness of using hsCRP to select patients for lipid-lowering treatment is not known.

ADDITIONAL TREATMENT RECOMMENDATIONS

- 1 Do not use hsCRP to monitor or adjust lipid-lowering therapy.
- 2 Because of the increased potential for myopathy, reduced initial doses of statins, fibrates and niacin should be considered in people with GFR <30 mL/min/1.73 m², in medically complicated people, the very elderly, people taking interacting drugs or using combination lipid-modifying therapy. Statin doses can be cautiously increased, even up to maximal doses, if benefit exceeds risk.
See CKD Section and Statin section of Table 3 for additional information.
- 3
 - ◆ If the LDL-C is not below target after 6-8 weeks, advance therapy per the following protocol:
 - ▶ Simvastatin 40 mg
 - ▶ Simvastatin 80 mg
 - ◆ Further options beyond simvastatin 80 mg include:
 - ▶ Combine simvastatin 80 mg with:
 - ▶ Niacin
 - ▶ Ezetimibe (Vytorin 10/80)
 - ▶ Resins
 - ▶ Plant stanols/sterols
 - ▶ Switch to other statins (atorvastatin 80 mg, rosuvastatin 40 mg [non-formulary])
 - ▶ Stop advancing therapy
 - ▶ Seek lipid specialist consultation
- 4 After achievement of LDL-C goal, repeat the lipid panel annually to ensure that the patient remains at goal. (It is optional to retest in 3-6 months.)

Detection and Evaluation

(continued)

4 Use of hsCRP Test

- ◆ The hsCRP test has no role and should not be ordered in people where statin therapy is already recommended. (See Table 2 for recommendations on appropriate use of hsCRP test.)
- ◆ The hsCRP test should not be used to monitor or adjust lipid-lowering therapy for primary or secondary prevention patients.
- ◆ In men age 50 or older and women age 60 or older who are not selected for treatment based on the '10-Year CAD Risk' tables, it is **OPTIONAL** to measure hsCRP, and if hsCRP is ≥ 2 mg/L on two tests, to initiate simvastatin 40 mg daily.
- ◆ The hsCRP test should only be ordered if the result will prompt a therapeutic decision and the clinician and patient have agreed to initiate statin therapy if the result is high, and to forgo statin therapy if the result is low.

While elevated hsCRP is considered an emerging risk factor for CAD, there is conflicting evidence as to whether the addition of hsCRP testing significantly improves the ability of Framingham risk equations to predict CVD risk for primary prevention patients. The GDT's decision to support optional use of hsCRP testing in some patients is not based on the improvements that hsCRP adds to Framingham, but rather on the direct evidence from the JUPITER trial which showed that hsCRP results can be used to identify lower risk primary prevention men age ≥ 50 and women age ≥ 60 who would benefit from statin therapy.

ORDERING AND INTERPRETATION OF HSCRP TEST

The standard CRP test is not useful for cardiac risk assessment and should not be ordered for this purpose. The correct test is the high-sensitivity CRP, sometimes called the 'cardio CRP' or 'wide range CRP.'

- ◆ hsCRP should be ordered only in metabolically stable patients who are free of active infection, systemic inflammation*, recent trauma and are not on estrogen therapy, immunosuppressants or glucocorticoids.
- ◆ If hsCRP is ≥ 2 mg/L, repeat hsCRP two weeks later. Statin therapy contingent on hsCRP is only recommended if two hsCRP tests are both ≥ 2 mg/L.
- ◆ If hsCRP is >10 mg/L, the patient should be evaluated for sources of infection or inflammation and the test repeated.

*Examples of inflammatory conditions that could invalidate the test results are rheumatoid arthritis, lupus and inflammatory bowel disease. Patients with osteoarthritis should not be excluded.

Management

5 Lifestyle Modification

- ◆ **Strongly encourage tobacco cessation, increased physical activity, and a diet that is low in saturated fat, Mediterranean, and regularly contains fish with high omega-3 content** (e.g., two servings per week of salmon, herring, tuna, sardines and mackerel [except king mackerel which may have excessive mercury content]). See the **KPNC CAD Clinical Practice Guideline** for more information on lifestyle modifications for secondary prevention.
- ◆ **There is currently insufficient evidence to recommend for or against low-carbohydrate diets for the prevention of atherosclerotic disease.**
- ◆ **Promoting alcohol consumption in people with or without atherosclerotic disease is NOT recommended because of the risk of developing alcohol-related problems.**

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 red 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 Mediterranean or diets regularly containing fish with high omega-3 content are also effective for primary prevention of atherosclerosis. In addition to replacing saturated fats from red meat, high omega-3 fish diets are also a source of high-quality protein, vitamins and minerals. (See the **Fish Oil Supplements** section for more information on fish oils.)

Management

(continued)

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.)

6 Lipid Treatment Goals for Primary Prevention

An LDL-C treatment goal of <130 mg/dL is recommended for primary prevention people who are at sufficient risk to warrant statin treatment. The evidence from randomized controlled trials (RCTs) seems to indicate a linear relationship between achieved LDL-C and risk of CAD events. However, there is no direct evidence from RCTs comparing different LDL-C targets in primary prevention. The JUPITER trial did not evaluate LDL-C treatment thresholds or targets and should not be used to infer the optimal LDL-C thresholds and targets for primary prevention. The GDT agreed by consensus that an LDL-C <130 mg/dL is appropriate in primary prevention people. 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 (see **High TG Level** in section 11). After LDL-C is at goal, a non-HDL cholesterol goal of <160 mg/dL is recommended (non-HDL cholesterol is total cholesterol minus HDL-C).

For primary prevention people with non-coronary atherosclerotic disease, 10-year CAD Risk > 20%, NKF CKD Stage 4 or 5, ischemic stroke/TIA, and diabetes mellitus, an LDL-C treatment goal of < 100 mg/dL is recommended. A non-HDL cholesterol goal of <130 mg/dL is recommended after LDL-C is at goal. If the target LDL-C is difficult to obtain, use clinical judgment to weigh the benefits and risks of intensifying drug therapy.

7 Lipid Treatment Goals for Secondary Prevention

An LDL-C treatment goal of <100 mg/dL is recommended for reducing rates of coronary events in patients with established atherosclerotic disease. 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 (see **High TG Level** in Section 11).

A more aggressive LDL-C goal of <70 mg/dL is an option. With the increasing use of more potent statins, there are now many randomized controlled trials where the treatment group has attained LDL-C levels substantially below 100 mg/dL. Several have obtained levels below 70 mg/dL. In all cases the lower LDL-C group had significantly fewer atherosclerotic events. Most of these trials, however, were not designed to evaluate the LDL-C level obtained and it is therefore unknown whether the benefit was derived from the LDL-C reduction, the potency of the statin, other factors, or a combination of these. The Guideline Development team therefore recommends the goal of LDL-C <70 as an option. Many authorities, however, now recommend the <70 mg/dL goal especially in patients at very high risk.

When to intensify treatment in people with an LDL-C <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 cholesterol, medication tolerance, cost and patient preference.

8 Choice of Drug — Primary and Secondary Prevention

Before initiating drug treatment, rule out and, if present, correct any secondary causes of dyslipidemia such as poor glycemic control, hypothyroidism, renal or liver disease, or medications.

Because of its proven effectiveness in event reduction, safety and cost, simvastatin is the preferred first-line statin for both primary and secondary prevention patients. Comparisons of individual lipid lowering therapies (statins, resins, fibrates and niacin) vs. placebo have shown that statins are the most effective for reducing CVD events. Given that all statins appear to be efficacious at lowering LDL-C, the choice of simvastatin is based on both cost and evidence of direct benefit on important health outcomes (e.g., CVD morbidity and mortality). The initiation doses in **Table 2** were chosen to achieve target LDL-C, up to the maximum dose of 80 mg daily. See **Table 3** for dosing and safety recommendations for the use of lipid modifying drugs.

Management

(continued)

9 Lipid Management in Acute Coronary Syndromes

In patients with acute coronary syndrome:

- ◆ Statins are recommended regardless of baseline LDL-C.
- ◆ If baseline lipid values are desired, a 12-hour fasting lipid panel is recommended as soon as possible, but definitely within 48 hours after hospital admission.
- ◆ If a fasting lipid panel is not possible, a non-fasting lipid panel is recommended as soon as possible after hospital admission.
- ◆ Repeat the lipid panel two months after hospital discharge.

The stress of acute events can lower LDL-C levels for up to 2 to 3 months. Evidence suggests that people with ACS should receive immediate aggressive statin lipid-lowering treatment. Emphasize the importance of lifestyle modifications and adherence to lipid-lowering medications.

10 Special Populations

A. METABOLIC SYNDROME

People with metabolic syndrome, are at increased risk for CAD. According to a definition adapted from NCEP ATP III, metabolic syndrome is defined by the presence of three or more of the following:

- ◆ **Abdominal Obesity** – defined as:
 - ▶ waist circumference >40 inches (102 cm) in men, and >35 inches (88 cm) in women (waist circumference is the ATP III criterion), **OR**
 - ▶ BMI ≥ 30 kg/m² (BMI is the World Health Organization criterion)
- ◆ Triglycerides ≥ 150 mg/dL
- ◆ HDL-C <40 mg/dL for men or <50 mg/dL for women
- ◆ Blood Pressure $\geq 130/85$ mmHg
- ◆ Fasting Plasma Glucose 100-125 mg/dL

NOTE: Above-normal FPG may imply insulin resistance; the American Diabetes Association has adopted normal FPG <100 mg/dL, ATP III uses FPG <110 mg/dL.

There is indirect evidence that the metabolic syndrome is associated with increased risk of CAD, 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 from those determined by the traditional risk factors.

It is beyond the scope of this dyslipidemia guideline to recommend treatment for all the components of the metabolic syndrome. 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. After the LDL-C goal is achieved, non-HDL cholesterol can be targeted. Many of these people may require combination therapy to achieve both LDL-C and non-HDL cholesterol goals. See **Specific Dyslipidemias** section, **Table 2** and **Figure 1** 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 optional LDL-C treatment goal of <70 mg/dL and the optional non-HDL cholesterol goal of <100 mg/dL.

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 cholesterol targets easier.

B. ELDERLY — AGE 65 OR OLDER

Evidence from randomized controlled trials indicates that people between age 65 and 85 benefit from lipid lowering. The effectiveness and benefits of drug therapy seen in this population are essentially the same as seen in people under age 65. The decision to treat should be based on a person's lipid and nonlipid CAD risk factors and physiologic rather than chronologic age. 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 3**).

Management

(continued)

C. DIABETES MELLITUS AGE 40 OR OLDER

Both the Heart Protection Study and the Collaborative Atorvastatin Diabetes Study (CARDS) showed that people with diabetes and without established CAD are at high risk and derive a large benefit from statin treatment, regardless of baseline LDL-C. Based on these data, statin therapy is recommended, regardless of baseline LDL-C. As in CAD, these trials were not designed to determine the optimal target LDL-C. An LDL-C goal of <100 mg/dL, with an optional goal of <70 mg/dL, is recommended for all people with diabetes age 40 or older.

D. DIABETES MELLITUS AGE 39 OR YOUNGER

For people with diabetes age 39 or under, there are no studies that examine the effects of lipid-lowering on CAD outcomes. Furthermore, the **10-Year CAD Risk** tables (derived from the ATP III Framingham risk calculator) do not estimate risk for people with diabetes. However, it is well-recognized that people with diabetes are at much higher risk for CAD than those without diabetes. The Guideline Development Team considered the contribution of other risk factors in this population and made the following recommendations:

For people with diabetes under age 39 or younger **WITH** ≥ 1 risk factor*:

- ◆ Statin therapy is **RECOMMENDED** when LDL-C ≥ 100 mg/dL
- ◆ Statin therapy is **OPTIONAL** when LDL-C <100 mg/dL

For people with diabetes under age 39 or younger **WITHOUT** risk factors*:

- ◆ Statin therapy is **RECOMMENDED** when LDL-C ≥ 130 mg/dL
- ◆ Statin therapy is **OPTIONAL** when LDL-C <130 mg/dL

* Risk factors include: duration of diabetes ≥ 10 years, HDL-C <40 mg/dL, current smoker or family history of premature CAD (Clinical CAD or sudden death in a first-degree relative aged <55 (men) and <65 (women))

E. CHRONIC KIDNEY DISEASE

People with CKD, including NKF Stages 1, 2 and 3, are at increased risk for 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 are emerging data that suggest a GFR 30-44 imparts a significantly increased risk for CVD, but not equivalent to the risk of people with established CAD. Therefore our current recommendations for people with NKF stages 1, 2 and 3 remains unchanged: there is insufficient evidence that people with CKD stages 1, 2 or 3 should be treated differently on the basis of their CKD status alone. There is evidence that people with CKD stages 4 or 5 are at sufficiently high risk to be considered CAD Risk Equivalents. Therefore, treatment is **RECOMMENDED** in people with CKD Stages 4 or 5 if baseline LDL-C ≥ 100 and treatment is **OPTIONAL** if LDL-C is <100 mg/dL. The goal LDL-C is <100 mg/dL. See **Tables 2 and 3** for dosing and safety recommendations for the use of lipid modifying drugs in CKD patients.

11 Special Dyslipidemias

A. HIGH HDL-C

An HDL-C level of ≥ 60 mg/dL is considered by the NCEP ATP III to be a 'negative risk factor' that may counterbalance a positive risk factor. A high HDL-C level, however, is not always protective. The function of HDL-C, which is currently not readily measurable, may contribute to HDL-C's benefit, or lack of benefit, and is likely as important as the total amount. A high HDL-C level does not eliminate risk and therefore should not remove the focus from treating high LDL-C levels regardless of the HDL-C level.

Management

(continued)

B. VERY HIGH LDL-C

People with LDL-C ≥ 190 mg/dL are at high risk for CAD and treatment is recommended, regardless of other risk factors, unless there are compelling reasons against it. Treatment that lowers LDL-C is especially indicated in the presence of other risk factors, particularly a family history of premature CAD.

C. LOW HDL-C

HDL-C < 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 modestly increase HDL-C.

D. HIGH NON-HDL CHOLESTEROL — TC MINUS HDL-C

Non-HDL cholesterol comprises all the cholesterol carried by potentially atherogenic particles, which, when TG's are ≥ 200 mg/dL may be a substantial amount. Therefore, once LDL-C is at goal, if the TG level is ≥ 200 mg/dL, non-HDL cholesterol should be brought to goal. The non-HDL cholesterol goal is 30 mg/dL above the LDL-C goal. Weight reduction and physical activity are recommended; drug therapy to attain this goal includes those agents that lower either LDL-C or TG's.

E. HIGH TG LEVEL

There is evidence that elevated TG is independently associated with increased risk of atherosclerosis. However, not all people with high TGs are at increased risk, and neither the threshold for initiation of therapy, nor the goal of therapy, is known. Although there is direct evidence that lowering LDL-C reduces the risk of CAD events, there are no clinical trials to demonstrate that reducing TG levels will reduce CAD events. There is expert opinion that a desirable TG level is < 150 mg/dL, but there are no studies to support the benefit of obtaining this level. 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 ≥ 500 mg/dL warrants treatment to prevent pancreatitis. Specific recommendations for treating high TG level are presented in **Figure 1** below.

Management

(continued)

Fish Oil Supplements

Fish oils have important effects on TGs and LDL-C. See Table 3 for information regarding the effects of fish oils on TG.

- ◆ Fish oil supplements (~1 g/day of eicosapentaenoic acid/docosahexaenoic acid [EPA/DHA]) are optional for post-MI patients for the purpose of reducing CAD events.
- ◆ There is insufficient evidence to recommend for or against fish oil supplements for the purpose of reducing CAD events in people who have not had an MI.

For people with existing CAD, there are conflicting RCT data regarding the effectiveness of fish oil supplements for reducing mortality and CAD events. While one large clinical trial (GISSI-P) has shown that a fish oil supplement can reduce total and cardiac mortality in post-MI patients, it is uncertain from meta-analyses of secondary prevention trials whether high fish oil consumption has any significant effect on the risk of CAD events. Additionally, OTC fish oil supplements—not regulated by the FDA—contain widely varying omega-3 fatty acid content with different EPA/DHA ratios. As a result of these factors, the GDT consensus is that the use of fish oil supplements in post-MI patients is optional.

Adult Cholesterol Management

Management

(continued)

Adjunctive Therapy

ASPIRIN TREATMENT

Use of Aspirin for Primary CVD Prophylaxis:

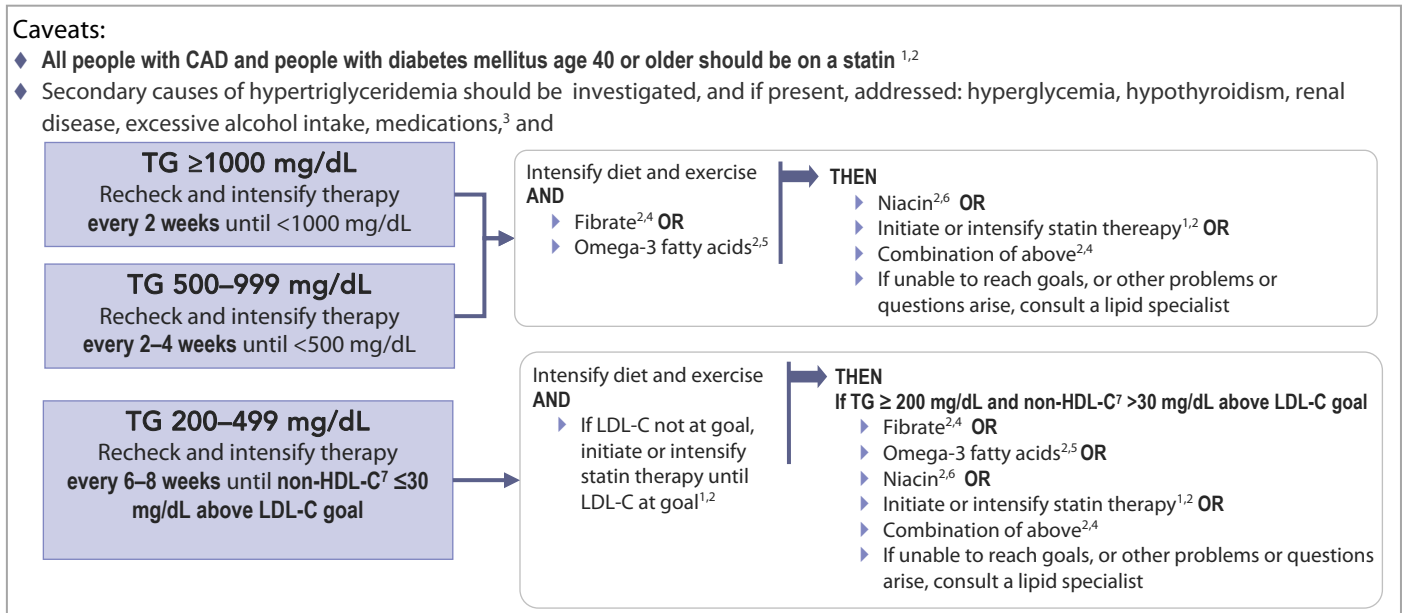
- ◆ **In the absence of known CAD, stroke or DM:**
 - ▶ When the CAD risk is high*, low dose aspirin (81 mg daily) is recommended.
 - ▶ For individuals with an intermediate risk* of CAD, discuss low dose aspirin (81 mg daily) as adjunctive therapy. Use of aspirin should be based on each individual’s benefit/risk** status.
 - ▶ When the CAD risk is low*, the benefits of aspirin are unlikely to outweigh the risks.
- ◆ **Uncontrolled hypertension is a relative contraindication to aspirin primary prophylaxis.**
- ◆ **Consider underlying risk for coronary heart disease, as well as the relative values patients attach to the main outcomes when discussing aspirin with potential candidates.**

* According to the Kaiser Permanente **10-Year CAD Risk** tables: low risk is <10%, intermediate risk is 10-20%, and high risk is >20%.

** The benefit for men is primarily reduction in nonfatal MI and the benefit for women is stroke reduction. Low dose aspirin increases the risk for GI bleeding and hemorrhagic stroke, and the risk for hemorrhagic stroke may increase with uncontrolled hypertension, particularly stage 2 hypertension. NNTs to prevent one adverse CV outcome vs. NNHs (usually a GI bleed requiring transfusion) for men and women on low dose aspirin for primary CV prophylaxis for 6.4 years are: men: NNT 270 and NNH 303; women NNT 333 and NNH 400. For 1000 patients at high CAD risk, aspirin would prevent 6-20 nonfatal MIs, but would cause 0-2 hemorrhagic strokes and 2-4 major GI bleeds. For patients at low CAD risk, aspirin would prevent 1-4 MIs but would cause 0-2 hemorrhagic strokes and 2-4 major GI bleeds.)

Continuing research has validated the recommendation regarding the use of aspirin as concomitant therapy for patients with controlled hypertension. Based on the information and evidence presented, the GDT concluded that among people with controlled hypertension, the use of aspirin therapy for primary CVD prophylaxis should be based on individual CAD risk levels.

FIGURE 1: Triglyceride (TG) Treatment Recommendations



1. A minimum dose of simvastatin 40 mg is recommended if GFR ≥30 ml/min (see Table 2).
 2. See **Medication Information** and **Lipid-lowering Drugs: Medication Efficacy, Safety and Cost** sections for more information on specific drugs and drug combinations.
 3. Beta-blockers, bile acid sequestrants, estrogens, etretinate, immunosuppressants, isotretinoin, prednisone, protease inhibitors and thiazide diuretics can raise triglyceride levels.
 4. Caution is advised for statin-niacin and statin-fibrate combinations (i.e., begin with reduced statin dose, and carefully titrate, if warranted). Use fenofibrate if patient is on a statin, use gemfibrozil if not on a statin.
 5. Dose for TG-lowering is 2-4 gm/day of DHA-EPA content.
 6. Maximum dose for sustained release (SR) niacin monotherapy is 2 gm/day. Slo-Niacin® is the preferred formulary SR niacin agent.
 7. Non-HDL-C = Total Cholesterol minus HDL-C.

TABLE 3: Lipid-Lowering Medications — Medication Efficacy, Safety, Cost and Comments

HMG-CoA REDUCTASE INHIBITORS (STATINS)					
<p>INDICATIONS: High LDL-C, CAD, CAD Risk Equivalent, DM age 40 or older. Statins 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. See Table 2 for initial doses and other treatment considerations. For each doubling of the dose, an additional LDL-C reduction of approximately 6-7% is expected. TG reductions as well as increases in HDL-C vary as a function of statin dose and baseline TG and HDL-C levels. If goals are not reached at maximum statin dose and potency, consider combination therapy (adding niacin, ezetimibe, resins or stanols/sterols) or referral to a lipid specialist. (See Combination Therapy section below.)</p> <p>RECOMMENDED STATIN: Based on evidence of efficacy, safety and cost, simvastatin is the preferred Formulary statin. For optimal LDL-C reduction, administer simvastatin daily in the evening.</p> <p>LIVER SAFETY: When significantly elevated aminotransferase levels 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. Statins may be used in people with fatty liver/nonalcoholic steatohepatitis (NASH) if their serum aminotransferase levels are <3 x ULN and stable.</p> <p>It is important that patients for whom statin therapy is recommended understand that they are at far greater risk from cardiovascular disease than from statin-induced liver injury. Nonetheless, it is prudent to delay the initiation of statins (and many other medications) in people who have active liver disease until disease stability is demonstrated. We therefore recommend obtaining a baseline ALT before starting statin therapy. To be conservative, we also recommend rechecking the ALT level 6 weeks after</p>					
<p>treatment initiation and after each dosage increase. Stop the statin if the ALT increases to >3 x ULN.</p> <p>MUSCLE SYMPTOMS: Though infrequent, significant generalized muscle aches and/or weakness can occur with statin use in a dose-related fashion. 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. Therefore, we do not recommend routine monitoring of CK, but rather recommend counseling the patient to report significant generalized muscle symptoms.</p> <p>MANAGEMENT RECOMMENDATIONS: If a patient on a statin experiences either ALT >3 x ULN or persistent 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.</p> <ul style="list-style-type: none"> ▶ 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 because of low cost. Pravastatin is an alternative, recommended on the theoretical basis of its hydrophilicity and minimal interactions with CYP 3A4 inhibitors. 					
STATIN DOSING The five statins listed below have good CVD outcome data available	LDL-C EFFECTS	HDL-C EFFECTS	TG EFFECTS	COST /YR*	SAFETY COMMENTS
SIMVASTATIN — ZOCOR					
10 mg daily	27% ↓	5-15% ↑	7-30% ↓	\$	<p>SIDE EFFECTS: flatulence (<5%), constipation (<5%), headache (<4%), myalgia (<3%), abdominal pain/cramping (2-3%), weakness (<2%), nausea (<2%), elevated serum aminotransferase (1-2%), and muscle cramps (<1.5%).</p> <p>MYOPATHY and potentially fatal rhabdomyolysis are rare side effects. The risk is increased in people who are also prescribed interacting drugs, people who are frail or have medical complications, the very elderly, and people with impaired renal function. For these people, consider initiating therapy with reduced doses, and increasing cautiously if benefit exceeds risk.</p> <p>POTENT INHIBITORS OF CYP 3A4: Because risk of muscle injury is related to statin exposure, the use of erythromycin, clarithromycin, azole antifungals (ketoconazole, itraconazole), nefazodone, protease inhibitors, or regular consumption of >1 quart/day of grapefruit juice is not recommended with lovastatin, simvastatin, and NF-atorvastatin. Pravastatin and NF-rosuvastatin have a theoretical advantage for people on chronic therapy with the above medications based on a decreased potential for adverse CYP 3A4-mediated drug interactions.</p> <p>OTHER DRUGS: For people taking cyclosporine, verapamil, diltiazem, or amiodarone, consider switching to alternate medications before initiating statins. If those medications need to be continued or for people taking fibrates, or niacin ≥1000 mg daily, initiate statins in lower doses and increase cautiously if benefit exceeds risk.</p> <p>CKD STAGE 4 OR 5: In people with GFR <30 mL/min/1.73 m², initiate simvastatin 20 mg daily in the evening. Statin doses may be cautiously increased, up to maximal doses, if benefit exceeds risk.</p> <p>CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum aminotransferase levels and pregnancy and lactation. For women of child-bearing potential who elect to initiate statin therapy, contraception and/or Plan B should be discussed and prescribed.</p>
20 mg daily	34% ↓			\$	
40 mg daily	41% ↓			\$	
80 mg daily	47% ↓			\$	
LOVOSTATIN — MEVACOR					
10 mg daily	20% ↓	5-15% ↑	7-30% ↓	\$	<p>POTENT INHIBITORS OF CYP 3A4: Because risk of muscle injury is related to statin exposure, the use of erythromycin, clarithromycin, azole antifungals (ketoconazole, itraconazole), nefazodone, protease inhibitors, or regular consumption of >1 quart/day of grapefruit juice is not recommended with lovastatin, simvastatin, and NF-atorvastatin. Pravastatin and NF-rosuvastatin have a theoretical advantage for people on chronic therapy with the above medications based on a decreased potential for adverse CYP 3A4-mediated drug interactions.</p> <p>OTHER DRUGS: For people taking cyclosporine, verapamil, diltiazem, or amiodarone, consider switching to alternate medications before initiating statins. If those medications need to be continued or for people taking fibrates, or niacin ≥1000 mg daily, initiate statins in lower doses and increase cautiously if benefit exceeds risk.</p> <p>CKD STAGE 4 OR 5: In people with GFR <30 mL/min/1.73 m², initiate simvastatin 20 mg daily in the evening. Statin doses may be cautiously increased, up to maximal doses, if benefit exceeds risk.</p> <p>CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum aminotransferase levels and pregnancy and lactation. For women of child-bearing potential who elect to initiate statin therapy, contraception and/or Plan B should be discussed and prescribed.</p>
20 mg daily	27% ↓			\$	
40 mg daily	34% ↓			\$	
80 mg daily (2 x 40 mg tablets)	41% ↓			\$	
PRAVASTATIN — PRAVACHOL					
10 mg daily	20% ↓	5-15% ↑	7-30% ↓	\$	<p>POTENT INHIBITORS OF CYP 3A4: Because risk of muscle injury is related to statin exposure, the use of erythromycin, clarithromycin, azole antifungals (ketoconazole, itraconazole), nefazodone, protease inhibitors, or regular consumption of >1 quart/day of grapefruit juice is not recommended with lovastatin, simvastatin, and NF-atorvastatin. Pravastatin and NF-rosuvastatin have a theoretical advantage for people on chronic therapy with the above medications based on a decreased potential for adverse CYP 3A4-mediated drug interactions.</p> <p>OTHER DRUGS: For people taking cyclosporine, verapamil, diltiazem, or amiodarone, consider switching to alternate medications before initiating statins. If those medications need to be continued or for people taking fibrates, or niacin ≥1000 mg daily, initiate statins in lower doses and increase cautiously if benefit exceeds risk.</p> <p>CKD STAGE 4 OR 5: In people with GFR <30 mL/min/1.73 m², initiate simvastatin 20 mg daily in the evening. Statin doses may be cautiously increased, up to maximal doses, if benefit exceeds risk.</p> <p>CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum aminotransferase levels and pregnancy and lactation. For women of child-bearing potential who elect to initiate statin therapy, contraception and/or Plan B should be discussed and prescribed.</p>
20 mg daily	27% ↓			\$	
40 mg daily	34% ↓			\$	
80 mg daily	41% ↓			\$	
NF-ATORVASTATIN — LIPITOR-B					
10 mg daily (use ½ 20 mg tablet)	34% ↓	5-9% ↑	7-30% ↓	\$\$\$	<p>POTENT INHIBITORS OF CYP 3A4: Because risk of muscle injury is related to statin exposure, the use of erythromycin, clarithromycin, azole antifungals (ketoconazole, itraconazole), nefazodone, protease inhibitors, or regular consumption of >1 quart/day of grapefruit juice is not recommended with lovastatin, simvastatin, and NF-atorvastatin. Pravastatin and NF-rosuvastatin have a theoretical advantage for people on chronic therapy with the above medications based on a decreased potential for adverse CYP 3A4-mediated drug interactions.</p> <p>OTHER DRUGS: For people taking cyclosporine, verapamil, diltiazem, or amiodarone, consider switching to alternate medications before initiating statins. If those medications need to be continued or for people taking fibrates, or niacin ≥1000 mg daily, initiate statins in lower doses and increase cautiously if benefit exceeds risk.</p> <p>CKD STAGE 4 OR 5: In people with GFR <30 mL/min/1.73 m², initiate simvastatin 20 mg daily in the evening. Statin doses may be cautiously increased, up to maximal doses, if benefit exceeds risk.</p> <p>CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum aminotransferase levels and pregnancy and lactation. For women of child-bearing potential who elect to initiate statin therapy, contraception and/or Plan B should be discussed and prescribed.</p>
20 mg daily (use ½ 40 mg tablet)	41% ↓	5-9% ↑		\$\$\$	
40 mg daily (use ½ 80 mg tablet)	47% ↓	2-5% ↑		\$\$\$	
80 mg daily	54% ↓	2-5% ↑		\$\$\$\$	
NF-ROSUVASTATIN — CRESTOR-B					
5 mg daily	40% ↓	8-14% ↑	10-35% ↓	\$\$\$\$\$	<p>POTENT INHIBITORS OF CYP 3A4: Because risk of muscle injury is related to statin exposure, the use of erythromycin, clarithromycin, azole antifungals (ketoconazole, itraconazole), nefazodone, protease inhibitors, or regular consumption of >1 quart/day of grapefruit juice is not recommended with lovastatin, simvastatin, and NF-atorvastatin. Pravastatin and NF-rosuvastatin have a theoretical advantage for people on chronic therapy with the above medications based on a decreased potential for adverse CYP 3A4-mediated drug interactions.</p> <p>OTHER DRUGS: For people taking cyclosporine, verapamil, diltiazem, or amiodarone, consider switching to alternate medications before initiating statins. If those medications need to be continued or for people taking fibrates, or niacin ≥1000 mg daily, initiate statins in lower doses and increase cautiously if benefit exceeds risk.</p> <p>CKD STAGE 4 OR 5: In people with GFR <30 mL/min/1.73 m², initiate simvastatin 20 mg daily in the evening. Statin doses may be cautiously increased, up to maximal doses, if benefit exceeds risk.</p> <p>CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum aminotransferase levels and pregnancy and lactation. For women of child-bearing potential who elect to initiate statin therapy, contraception and/or Plan B should be discussed and prescribed.</p>
10 mg daily	46% ↓	8-14% ↑		\$\$\$\$\$	
20 mg daily	52% ↓	8-14% ↑		\$\$\$\$\$	
40 mg daily	56% ↓	8-14% ↑		\$\$\$\$\$	

NF Non-Formulary
B Brand copayment, no generic available
OTC Nonprescription, over-the-counter.

COST LEGEND (PER YEAR): \$: ≤\$100 \$\$: \$101 – 300 \$\$\$: \$301 – 600 \$ \$\$\$: \$601 – 1000 \$\$\$\$\$: >\$1000

* Costs are acquisition price/year (12/08) or OTC for niacin; patient costs against caps will be higher.

Adult Cholesterol Management

TABLE 3: Lipid-Lowering Medications — Medication Efficacy, Safety, Cost and Comments (continued)

NIACIN (NICOTINIC ACID)						
<p>INDICATIONS—High LDL-C, Low HDL-C, and/or High TG: Niacin lowers LDL-C and TG and is the most potent agent available for raising HDL-C. It has been shown to reduce CAD events, especially in combination with a statin in people with high CVD risk and low HDL-C.</p> <p>Careful dosage titration is required to promote tolerance and adherence to therapy. Flushing and pruritus can be minimized by slow up-titration, taking with meals, and taking aspirin (162-325 mg) or an NSAID (e.g., ibuprofen 200 mg) 30 minutes before each niacin dose.</p> <p>Niacin doses less than 2 grams/day generally include minimal and transient increases in glucose and HbA1c that are amenable to slight adjustments of oral antidiabetic drugs or insulin. Improved cardiovascular outcomes with niacin treatment have been demonstrated in people both with and without</p>		<p>diabetes. Sustained-release niacin is generally better tolerated than immediate-release preparations, and has been safely used in clinical trials at doses of up to 2000 mg daily (e.g., OTC Slo-Niacin in HATS).</p> <p>The maximum dose for sustained-release (OTC Slo-Niacin) and extended-release (NF-Niaspan) formulations is 2000 mg daily; if more niacin effects are desirable, switch to an immediate-release preparation and titrate further to a maximum of 3000 to 4500 mg daily in divided doses.</p> <p>Instruct patients to report symptoms of muscle injury (generalized muscle aches and/or weakness) or symptoms suggestive of liver toxicity (fatigue, nausea, anorexia). Serum aminotransferase levels, fasting blood sugar and uric acid levels should be monitored at baseline and periodically.</p>				
NIACIN DOSING	LDL-C EFFECTS	HDL-C EFFECTS	TG EFFECTS	COST /YR*	SAFETY COMMENTS	
IMMEDIATE-RELEASE NIACIN						
INITIAL DOSE: 50-100 mg/day Titrate slowly to 1000-3000 mg daily (in divided doses)	5-25% ↓	15-35% ↑	20-50% ↓	\$	<p>SIDE EFFECTS: Flushing, itching, tingling, headache, pruritus, and dyspepsia are common side effects that may limit adherence. Additional adverse effects include hepatotoxicity, loss of glycemic control, stomach ulcers, and increased uric acid.</p> <p>HEPATOXICITY and fatal hepatic necrosis have been reported with the OTC sustained-release niacin products, principally at high doses (> 2000 mg) without medical supervision or when patients were converted from immediate-release to sustained-release niacin on a mg:mg basis.</p> <p>DRUG INTERACTIONS: statins</p> <p>CONTRAINDICATIONS: Acute liver disease, active peptic ulcer disease, poorly controlled diabetes, and gout.</p>	
SUSTAINED-RELEASE NIACIN — SLO-NIACIN OTC						
500-2000 mg qHS or 500-1000 mg BID	5-25% ↓	15-35% ↑	20-50% ↓	\$\$-\$		
EXTENDED-RELEASE NIACIN — NF-NIASPAN-B						
500-1000 mg qHS	5-25% ↓	15-35% ↑	20-30% ↓	\$\$\$\$-\$\$\$\$\$		
FIBRIC ACID DERIVATIVES (FIBRATES)						
<p>INDICATIONS—High TG and/or Low HDL-C: Fibrates are effective at lowering TGs and modestly raising HDL-C. Fibrates have variable effects on LDL-C and sometimes increase it, particularly if baseline TGs are high.</p> <p>Clinical evidence from the VA-HIT study suggests that gemfibrozil provides benefit for secondary prevention people with a low HDL-C and without an elevated LDL-C.</p> <p>Because of the preponderance of statin clinical trial data, statins are the first-line drug choice for CVD prevention, even in people with a low HDL-C and without an elevated LDL-C. If TG ≥500 mg/dL in people with CAD, ischemic</p>		<p>stroke/TIA, AAA, PAD, significant carotid artery stenosis (>50%), or age 40 or older with DM, combination statin (to prevent CVD events) and TG-lowering therapy (to prevent pancreatitis) is recommended.</p> <p>Compared with 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 (≥ 500 mg/dL). The clinical significance of the resultant TG lowering and LDL-C increase is not known.</p>				
FIBRATE DOSING	LDL-C EFFECTS	HDL-C EFFECTS	TG EFFECTS	COST /YR*	SAFETY COMMENTS	
GEMFIBROZIL — LOPID						
600 mg BID AC	No change ↑ or ↓	10-35% ↑	20-50% ↓	\$	<p>SIDE EFFECTS: Dyspepsia, rash, abnormal liver function, gallstones, and rarely, with decreasing frequency, hepatitis, myopathy, and rhabdomyolysis. RHABDOMYOLYSIS has been reported with both gemfibrozil and fenofibrate monotherapy.</p> <p>DRUG INTERACTIONS: More data are needed to clearly define the overall efficacy and safety of fibrates when used in combination with statins. If combination therapy with a fibrate is required, an initial lower statin dose is recommended due to the increased risk of myopathy and rhabdomyolysis. Statin doses may be cautiously increased, up to maximal doses, if benefit exceeds risk. Fenofibrate is less likely to interact with statins than gemfibrozil and is preferred when combination therapy with statins is indicated. Both fenofibrate and gemfibrozil may increase the response to warfarin effects (monitor INR).</p> <p>CKD STAGES 4 AND 5: Use lower fibrate doses if GFR < 30 mL/min/1.73 m2. Reversible elevation of serum creatinine levels has been reported with both agents (higher with fenofibrate), but the clinical significance of this phenomenon is unclear.</p> <p>CONTRAINDICATIONS: Pre-existing gallbladder disease, hepatic dysfunction, or severe renal dysfunction.</p>	
FENOFIBRATE — GENERIC TRICOR, LOFIBRA						
Microcoated Tablets 54, 160 mg USUAL INITIAL DOSE: 160 mg daily with meal	No change ↑ or ↓	10-35% ↑	20-50% ↓	\$\$		

NF Non-Formulary
 B Brand copayment, no generic available
 OTC Nonprescription, over-the-counter.

COST LEGEND (PER YEAR): \$: ≤\$100 \$\$: \$101 – 300 \$\$\$: \$301 – 600 \$\$\$\$: \$601 – 1000 \$\$\$\$\$: >\$1000

* Costs are acquisition price/year (12/08) or OTC for niacin; patient costs against caps will be higher.

TABLE 3: Lipid-Lowering Medications — Medication Efficacy, Safety, Cost and Comments (continued)

BILE ACID SEQUESTRANTS					
<p>INDICATIONS—High LDL-C: Bile acid sequestering resins 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. No laboratory monitoring (other than lipid profiles) is necessary.</p> <p>Bile acid sequestrants are most effectively used in combination with other agents when further LDL-C reduction is required (see Combination Therapy), but should not be used when baseline TG \geq 200 mg/dL. Because</p>			<p>they can increase TG levels significantly (e.g., 20%). Combining a resin with a psyllium seed preparation may reduce GI side effects and further reduce the LDL-C.</p> <p>Colestipol and cholestyramine may be given once daily or in divided doses. Bulk generic cholestyramine powder is the least expensive formulation.</p>		
BILE ACID SEQUESTRANT DOSING	LDL-C EFFECTS	HDL-C EFFECTS	TG EFFECTS	COST /YR*	SAFETY COMMENTS
COLESTIPOL — COLESTID					
Powder for suspension (scoop) or 1 gram tablets				\$\$\$-\$\$\$\$\$	<p>SIDE EFFECTS: Constipation, dyspepsia, abdominal pain, bloating, belching, diarrhea, and nausea.</p> <p>DRUG INTERACTIONS: Bile acid sequestrants may interfere with the absorption of other oral medications (e.g., digoxin, , ezetimibe, levothyroxine, statins, vitamin K, warfarin); therefore, other medications should be taken one hour before or four hours after resins.</p> <p>CONTRAINDICATIONS: Complete biliary obstruction, bowel obstruction, or hypertriglyceridemia.</p>
CHOLESTYRAMINE — QUESTRAN					
Powder for suspension (scoop) 1 scoop (= 4 tablets) per day 2 scoops (= 8 tablets) per day 3 scoops (= 12 tablets) per day 6 scoops (max dose) per day	16% ↓ 23% ↓ 28% ↓ 33% ↓	0-5% ↑	0-20% ↓	\$\$-\$	
CHOLESTEROL ABSORPTION INHIBITORS					
<p>INDICATIONS—High HDL-C:</p> <p>EZETIMIBE: NF- ezetimibe inhibits dietary and biliary cholesterol absorption at the intestinal wall via its effect on brush border transporter proteins. Used as monotherapy at 10 mg daily, it reduces LDL-C by approximately 18%, though there is wide individual patient variation. 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, therefore statins, because of their proven outcome and safety data, remain the first-line therapy for people who require LDL-C reduction.</p> <p>EZETIMIBE-SIMVASTATIN (VYTORIN): Ezetimibe-simvastatin (Vytorin) is a combination tablet containing ezetimibe 10 mg and simvastatin in doses</p>			<p>ranging from 10 to 80 mg. It can provide marked LDL-C lowering (~60%). There are no outcome data to determine whether ezetimibe combined with simvastatin reduces CVD events better than simvastatin alone. To date, the large clinical trials evaluating the role of lipid-lowering therapy have demonstrated that lower LDL-C confers lower cardiovascular risk. Vytorin's demonstrated robust LDL-C lowering provides the rationale for using it to achieve large LDL-C reductions. Because the richest body of evidence that links lipid-lowering and CVD event reduction is for statin monotherapy, patients should first be titrated to the highest tolerated dose of a formulary statin in order to achieve their LDL-C target. For those who remain above target or cannot tolerate a high enough statin dose, combination ezetimibe-simvastatin is a reasonable treatment option. Vytorin is less expensive to use than separate prescriptions for any statin PLUS NF - ezetimibe.</p>		
CHOLESTEROL ABSORPTION INHIBITOR DOSING	LDL-C EFFECTS	HDL-C EFFECTS	TG EFFECTS	COST /YR*	SAFETY COMMENTS
NF-EZETIMIBE — ZETIA-B					
10 mg daily	18-20% ↓	0-5% ↑	5-10% ↓	\$\$\$	<p>EZETIMIBE</p> <p>SIDE EFFECTS: Myalgia, pain in extremity. In combination with statin may increase risk of aminotransferase elevation versus statins alone; however, in short-term clinical trials there was no excess of myopathy or rhabdomyolysis with combination ezetemibe/statin therapy versus statin alone.</p> <p>DRUG INTERACTIONS: Cyclosporine</p> <p>CONTRAINDICATIONS: Hypersensitivity to the medication.</p>
EZETIMIBE/SIMVASTATIN — VYTORIN-B					
10 mg/10 mg daily 10 mg/20 mg daily 10 mg/40 mg daily 10 mg/80 mg daily	45% ↓ 52% ↓ 55% ↓ 60% ↓	5-15% ↑	23-35% ↓	\$\$\$\$ \$\$\$\$ \$\$\$\$ \$\$\$\$	<p>EZETIMIBE/SIMVASTATIN</p> <p>Side effects, drug interactions and contraindications are the same for the two individual components (see 'statins' and 'ezetimibe')</p>

NF Non-Formulary
B Brand copayment, no generic available
OTC Nonprescription, over-the-counter.

COST LEGEND (PER YEAR): \$: \leq \$100 \$\$: \$101 – 300 \$\$\$: \$301 – 600 \$ \$\$\$\$: \$601 – 1000 \$\$\$\$: >\$1000

* Costs are acquisition price/year (12/08) or OTC for niacin; patient costs against caps will be higher.

Adult Cholesterol Management

TABLE 3: Lipid-Lowering Medications — Medication Efficacy, Safety, Cost and Comments (continued)

FISH OILS, OMEGA-3-ACID ETHYL ESTERS					
INDICATIONS AND DOSAGE:					
<p>VERY HIGH TRIGLYCERIDES (≥500 MG/DL): 4 gm (EPA + DHA) per day</p> <p>HISTORY OF MYOCARDIAL INFARCTION OR FOR 2° PREVENTION: 1 gm (EPA + DHA) per day.</p> <p>There is conflicting evidence regarding the use of fish oil supplements for CVD prevention, where a lower dose (1 gm/day) has been shown to reduce sudden death in post-MI patients. See Fish Oil Supplements section for further information.</p>		<p>Approximately 90% of the total omega-3 polyunsaturated fatty acid content of prescription-only NF - Lovaza is EPA + DHA as compared to a range of 30% - 65% for OTC fish oil supplements. Thus 1 gm Lovaza ≈ 2 - 3 gm of OTC products in terms of EPA + DHA content.</p> <p>Kaiser Permanente does not endorse NF - Lovaza or any of the OTC products. They are listed here to illustrate the variability of EPA + DHA content among different products as well as the wide range of costs.</p>			
DRUGS AND DOSING	LDL-C EFFECTS	HDL-C EFFECTS	TG EFFECTS	COST /YR*	SAFETY COMMENTS
FOR TRIGLYCERIDE >500 MG/DL REDUCTION					<p>SIDE EFFECTS: Dose-dependent potential for bleeding risk</p> <p>PRECAUTIONS: Increases in LDL-C of up to 45% have been observed in patients with very high TGs treated with 4 grams of fish oil supplements daily. The clinical significance of both the decrease in TGs and the increase in LDL-C is not known.</p> <p>DRUG INTERACTIONS: Patients receiving both high-dose fish oil concentrate supplements and anticoagulants should be monitored for bleeding complications.</p> <p>CONTRAINDICATIONS: Hypersensitivity to any component of the formulation.</p>
<p>NF-Omega-3-acid ethyl esters 1 gm capsule (Lovaza) – B (465 mg EPA + 375 mg DHA per capsule) ▶ 4 caps/day</p>	4-45% ↑	0-3% ↑	45% ↓	\$\$\$\$\$	
<p>NF-Kirkland Signature™ EC Fish Oil Concentrate 1200 mg Softgels – OTC (374 mg EPA + 310 mg DHA per capsule) ▶ 6 caps/day</p>	4-45% ↑	0-3% ↑	45% ↓	\$\$	
<p>NF-NVC Omega-3 Fish Oil/Vit E Soft Gels – OTC (180 mg EPA + 120 mg DHA + 5 IU Vit E) ▶ 12 caps/day</p>	4-45% ↑	0-3% ↑	45% ↓	\$\$	
FOR POST-MI OR SECONDARY PREVENTION					
<p>NF-Omega-3-acid ethyl esters 1 gm capsule (Lovaza) – B (465 mg EPA + 375 mg DHA per capsule) ▶ 1 caps/day</p>	No effect	No effect	No effect	\$\$\$	
<p>NF-Kirkland Signature™ EC Fish Oil Concentrate 1200 mg Softgels – OTC (374 mg EPA + 310 mg DHA per capsule) ▶ 2 caps/day</p>	No effect	No effect	No effect	\$	
<p>NF-NVC Omega-3 Fish Oil/Vit E Soft Gels – KP OTC (180 mg EPA + 120 mg DHA) ▶ 3 caps/day</p>	No effect	No effect	No effect	\$	

NF Non-Formulary
 B Brand copayment, no generic available
 OTC Nonprescription, over-the-counter.

COST LEGEND (PER YEAR): \$: ≤\$100 \$\$: \$101 – 300 \$\$\$: \$301 – 600 \$: \$601 – 1000 \$\$\$\$: >\$1000

* Costs are acquisition price/year (12/08) or OTC for niacin; patient costs against caps will be higher.

Acknowledgements

2010 DEVELOPMENT TEAM

ENDORSED BY

Chiefs of Medicine
Chiefs of Cardiology
Chiefs of Endocrinology

This guideline was developed by an interregional group of experts participating on the Adult Dyslipidemia Management Guideline Team, coordinated by the Kaiser Permanente Southern California (KPSC) Technology Assessment Group.

KPNC ADULT CHOLESTEROL MANAGEMENT GUIDELINE TEAM

Marc Jaffe, MD Medicine & Endocrinology, So San Francisco
Eleanor Levin, MD Cardiology, Santa Clara
Craig Sadur, MD Endocrinology, Pleasanton
Gary Besinque, PharmD Drug Information Services – Formulary, CA Regions

PROJECT MANAGEMENT

Joyce Arango
Quality and Operations Support

GRAPHIC DESIGN

Sharon Olsen
Quality and Operations Support

CONTACT INFORMATION

Kaiser Permanente Northern California
TPMG, Quality and Operations Support
1800 Harrison Street, 4th Floor
Oakland, CA 94612
510-625-6343 or tie line 8-428-6343

MORE INFORMATION

GUIDELINES AND IMPLEMENTATION TOOLS

KPNC Clinical Practice Guidelines and implementation tools are available on the QOS intranet website:

qos.har.ca.kp.org/CPG/cpg_guidelines.html

KPNC Clinical Practice Guidelines and implementation tools can also be viewed online on the KPNC Clinical Library intranet site at cl.kp.org

PUBLICATION REQUESTS

To obtain more information about KPNC Clinical Practice Guidelines, printed copies, or permission to reproduce any portion, please contact TPMG Quality and Operations Support at the number below or send an email message to Joyce.Arango@kp.org.

Phone: (510) 625-6343

FAX: (510) 625-7099

DISCLAIMER

The Permanente Medical Group (TPMG) Clinical Practice Guidelines have been developed to assist clinicians by providing an analytical framework for the evaluation and treatment of selected common problems encountered in patients. These guidelines are not intended to establish a protocol for all patients with a particular condition. While the guidelines provide one approach to evaluating a problem, clinical conditions may vary significantly from individual to individual. Therefore, the clinician must exercise independent judgment and make decisions based upon the situation presented. While great care has been taken to assure the accuracy of the information presented, the reader is advised that TPMG cannot be responsible for continued currency of the information, for any errors or omissions in this guideline, or for any consequences arising from its use. ■